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PULMONARY NITROGEN CLEARANCE IN THE FIRST TWO YEARS OF POLIOMYELITIS WITH RESPIRATORY MUSCLE PARALYSIS

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MANY disturbances of pulmonary function are recognized in acute anterior poliomyelitis with respiratory muscle paralysis. Lung compartition changes in poliomyelitis patients are readily detected and have been previously reported.[1-3] More complete studies of pulmonary function are needed to determine whether mixing abnormalities occur in patients with respiratory poliomyelitis. Since lung compartments are static volumetric measurements, they probably fail to reflect possible changes in lung gas mixing and distribution. Pulmonary nitrogen clearance while 100 per cent oxygen is breathed provides some index of this aspect of ventilatory efficiency.[4] Relating the nitrogen clearance to the functional residual capacity increases the precision of these measurements.[5-7] This may be studied with the nitrogen clearance technique reported by Luft, Roorbach, and MacQuigg.[6] Nitrogen elimination is quantitated in terms of the clearance equivalent (clearance ventilation divided by the functional residual capacity). Thus, the large variations in the magnitude of the functional residual capacity

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among different individuals are taken into account to some degree, since the nitrogen clearance is related to a unit of the resting or end expiratory lung volume.

The purpose of this article is to report the results obtained in a study of pulmonary nitrogen clearance during artificial respiration in patients with respiratory muscle paralysis due to poliomyelitis.

METHOD

Twenty men and 15 women who had poliomyelitis were included in this study. They had various degrees of respiratory muscle paralysis. The onset of poliomyelitis ranged from 17 days to 24 months prior to the time of this study. All of them had received artificial respiration at one time during their disease and all but 2 men and 2 women were still totally or partially dependent on mechanical breathing aid at the time of the test. The pulmonary nitrogen clearance was studied simultaneously with the determination of functional residual capacity by the use of an open circuit method which has been described previously.[3] One hundred per cent oxygen was used to wash out the lung nitrogen to the 1 per cent level according to the technique proposed by Luft, Roorbach, and MacQuigg.[6] Other lung compartments and elastic properties of the lungs and thorax were studied after the washout and the results were reported separately.[3,8]

In order to have conditions of ventilation as standardized as possible in the presence of variable degrees of residual respiratory muscle paralysis, the part of the study included in this report was carried out with the patient breathing in an Emerson tank respirator.* The respirator cycling rate was 15 per minute in every instance and the presssure settings were adjusted to duplicate closely the predicted steady-state ventilatory values obtained from the nomogram proposed by Radford.[9] Ventilation was monitored in a 9-L. Collins closed-circuit spirometer† which was connected prior to the washout.

The decreasing concentrations of nitrogen in the expired air during the washout were instantaneously detected by a nitrogen meter. The breath-by-breath deflections were recorded on an Esterline Angus recorder or on a Physiograph.[10] The records obtained were analyzed for the total washout time, the washout time to the 1 per cent level of expired nitrogen concentration, and the pattern of nitrogen elimination. Fig. 1 reproduces a record obtained from a poliomyelitis patient and it is compared with that obtained from a healthy person.

All the air expired by the subject from the time of initiation of the washout test was collected in a 120-L. Tissot spirometer. An attempt was made to interrupt the test as soon as a level of 1 per cent nitrogen was reached in the expired air, as determined by previous instrumental calibration. In some cases the washout was continued for a few more breaths, but in these instances the volume of oxygen required to reach the 1 per cent level of nitrogen could be estimated because the total volume of expiration, the total washout time, and the washout time to the 1 per cent level had been accurately measured. It should be emphasized that to make this calculation we assumed that the tidal volume of the subject was uniform throughout the washout test. Such an assumption is valid for the patient

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subjects, since they were subjected to artificial respiration at cycling rates and pressure settings which were unchanged during the procedures. Pre- and post-washout spirometric tracings of ventilatory volumes substantiated this.

"Clearance ventilation" is the total volume of expired air accumulated during breathing of 100 per cent oxygen until a level of 1 per cent nitrogen in the expired air is reached. The "clearance equivalent" is defined by Luft, Roorbach,

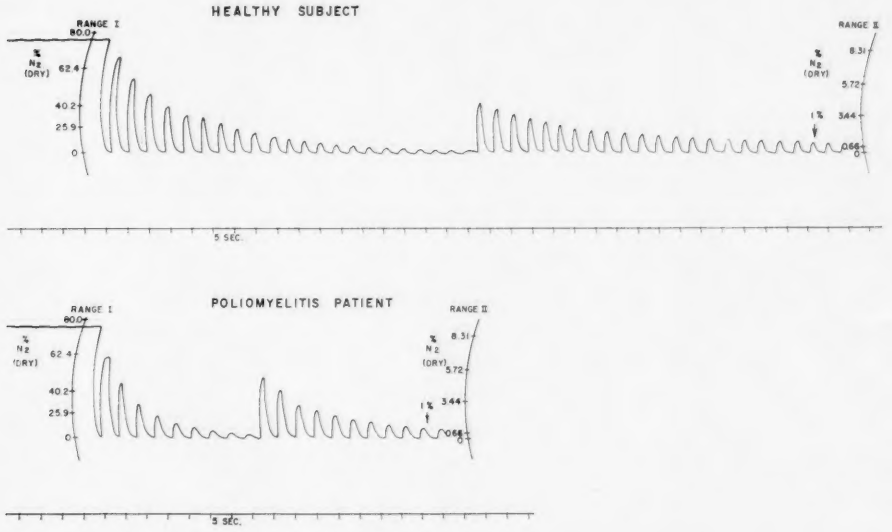

Fig. 1.—Pattern of nitrogen washout during breathing of 100 per cent oxygen in an open circuit. These records were obtained with a direct recorder, a Physiograph. The washout proceeds from left to right. The change in sensitivity of the instrument from range I to range II allows better recording of the low concentrations of nitrogen in expired air. The top record is that obtained in a healthy adult (C.V.) ranked number 15 of the healthy males; the bottom record is that obtained on a patient (B.C.) ranked number 15 of the female patients. The small variations in the deflection of the nitrogen meter during inspiration and expiration prior to breathing of oxygen are due to differences in the concentration of water vapor in the two phases of the breathing cycle. The addition of water vapor to the expired air represents a net decrease of the total number of molecules of nitrogen per unit of the volume which is sampled as a "wet sample" by the meter. The humidity of the inspired room air accounts for the discrepancy between the deflection of the meter at the time that the inspired air is sampled and the deflection given by a dry sample of 80 per cent nitrogen (as indicated in the calibration curve).

and MacQuigg[6] as the portion of "clearance ventilation" required to clear 1 L. of functional residual capacity to the 1 per cent level of nitrogen concentration at end expiration. It can be calculated according to the formula:

$$C_{EQ} = \frac{V_E \left(1 - \frac{V_D'}{V_T}\right)}{FRC}$$

In this formula C_{EQ} is the clearance equivalent, V_E is the clearance ventilation, V_D' is the part of the instrumental dead space that is being cleared of nitrogen during the washout, V_T is the average tidal volume during the procedure, and

FRC is the functional residual capacity. A correction is made in this equation for the volume of ventilation that is used for the clearance of the instrumental dead space. This may introduce a significant error if there is a large instrumental dead space in the circuit[11] or if tidal ventilation is shallow.

In this study the clearance ventilation was determined by the volume of expiration collected in the Tissot spirometer at the time the nitrogen concentration at the end of an expiration reached a 1 per cent level. A correction was made for the amount of air withdrawn for sampling in the nitrogen meter during the washout test (usually 0.03 L. per minute). The instrumental dead space cleared of nitrogen during the procedure was 0.12 L. in all the determinations. The tidal volume was calculated by dividing the volume of air expired during the washout by the total number of breaths during the procedure. The functional residual capacity was determined by use of the formula that we have previously reported.[3]

The values of functional residual capacity, clearance ventilation, clearance equivalent, and the FRC/TLC ratio obtained from the poliomyelitis patients were compared with those found previously in 25 healthy men and 25 healthy women of comparable age and physical characteristics studied during spontaneous breathing in the supine position. The apparatus used was identical in both groups. The only variation in method was the use of tank respirator respiration for the patients. The initiation of the washout test at resting expiratory level was secured by monitoring the ventilatory excursions in a 9-L. closed-circuit spirometer. Usually 2 to 3 minutes were required prior to the washout to obtain a steady and reasonably uniform pattern of breathing in the healthy persons.

The crude data of the respiratory function tests and the final results were tabulated with electronic data processing techniques.[12] This permitted rapid correction of lung volumes to BTPS conditions and simplified complete statistical analysis and correlation studies.

RESULTS

Tables I and II give the detailed physical characteristics, some lung compartment values, and lung gas distribution and mixing results for the healthy and patient groups, respectively. The subjects were ranked according to the magnitude of their FRC. These data are summarized in Table III. The values of other lung compartments for the healthy persons and for the majority of the patients have been reported elsewhere.[3] The difference in some physical characteristics (e.g., weight and body surface area in square meters) between healthy individuals and poliomyelitis patients is due to the weight loss and muscular atrophy that follows paralysis. The preillness body surface area and weight values of the patients are comparable to those of the healthy persons.

The values of clearance equivalent obtained in the healthy group of our series are quite similar to those obtained by Luft and associates in a larger series of healthy individuals measured in the sitting position.[12] Our values of clearance equivalent are slightly lower than those originally reported by the same authors, but no correction was made for the instrumental dead space in their original

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report.[6] The mean values of clearance equivalent reported by Luft[13] and by us are of a greater magnitude than those reported by Becklake[5] and Lundin.[7] The difference is due to the fact that the latter authors used the 2 per cent level of nitrogen at the end of an expiration as the end point of the washout test.

Values of clearance equivalent are less variable than those of clearance ventilation, and they are also reasonably independent of the values of tidal or minute ventilation and of the time of nitrogen washout to the 1 per cent level. The value of the clearance equivalent is not changed during steady-state ventilation in healthy individuals, because of changes in the functional residual capacity between the sitting and supine positions. The mean value of the clearance equivalent is practically identical for both sexes. For these reasons the use of the clearance equivalent in comparative studies of lung gas mixing appears to be practical. The lack of correlation between the clearance equivalent and the index RV/TLC or FRC/TLC as reported by Luft, Roorbach, and MacQuigg[6] is supported by the findings of our series of healthy persons.

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Table III includes the results of a significance test on differences obtained between patients and healthy persons for functional residual capacity, clearance ventilation, clearance equivalent, and the FRC/TLC ratio. The Mann-Whitney U test[14] was applied in each instance to test the null hypothesis that values on a particular variable were equally distributed among patients and healthy individuals. The probabilities (p) shown in the table are one-tailed probabilities reflecting the level of confidence at which the null hypothesis is rejected in favor of an alternative hypothesis. This alternate hypothesis would be that patient values for a particular variable are lower (or higher, depending upon the variable in question) than corresponding observations on healthy persons of the same sex. In all but one instance (the FRC/TLC ratio for women), differences between patients and healthy persons either reached or exceeded commonly accepted levels of significance.

DISCUSSION

This investigation of lung gas mixing and distribution revealed quantitative differences between supine individuals with respiratory muscle paralysis during artificial respiration and healthy persons breathing naturally. The nitrogen clearance equivalent was used as the best index of comparison available. For at least the first 2 years following onset of poliomyelitis, the results of nitrogen washout are opposite to those found in obstructive emphysema[6] and are frequently, but not invariably, lower than the values obtained in good health.

Significance of the Nitrogen Clearance Equivalent.—In good health, during steady-state breathing there is evidence that the inspired air is neither fully available to the alveoli nor equally distributed and mixed in amount or in location throughout the aerated lung tissue. Evidence for departure of pulmonary ventilation from perfect mixing behavior has been presented in several studies[15-18] and has been thoroughly discussed in a recent review article.[19] Two major factors appear to be important in the mixing and distribution of inspired air: (1) the anatomic dead space and (2) the differences in uniformity of inflation of various

TABLE I. DESCRIPTIVE DATA IN PULMONARY GAS DISTRIBUTION STUDIES IN HEALTHY YOUNG ADULTS

RANK	SUBJECT	AGE (YR.)	WEIGHT (LB.)	HEIGHT (IN.)	B.S.A. (SQ. M.)	FRC (L.)	CLEARANCE VENTILATION (L.)	TIDAL VOLUME (L.)	CLEARANCE EQUIVALENT	FRC / TLC	RV / TLC
Men											
1	H.V.	23	165	72.5	1.97	3.75	59.1	0.87	14.7	0.47	0.31
2	K.W.	38	160	69.5	1.89	3.70	47.2	0.85	11.4	0.49	0.34
3	G.M.	25	137	68.0	1.72	3.70	53.8	0.72	13.1	0.54	0.36
4	J.C.	23	190	72.0	2.09	3.57	67.7	0.82	18.1	0.43	0.32
5	J.F.	19	155	71.0	1.89	3.53	44.5	0.66	10.9	0.50	0.38
6	A.G.	25	188	70.5	2.03	3.52	46.9	1.00	12.2	0.45	0.20
7	R.J.	32	197	73.2	2.14	3.52	59.8	1.25	16.0	0.47	0.41
8	N.T.	26	138	68.0	1.77	3.39	42.5	1.00	11.3	0.47	0.31
9	J.M.	22	170	68.5	1.91	3.37	34.0	0.80	8.9	0.43	0.26
10	Y.M.	28	130	68.0	1.71	3.30	36.2	0.65	9.4	0.46	0.29
11	R.C.	24	165	70.0	1.92	3.27	48.6	0.63	13.2	0.48	0.34
12	G.H.	35	135	67.0	1.71	3.14	50.9	0.62	14.9	0.46	0.29
13	J.M.	27	150	68.0	1.82	3.11	55.4	0.47	14.4	0.54	0.41
14	J.J.	28	145	68.5	1.79	3.10	41.3	0.62	11.7	0.53	0.36
15	C.V.	30	163	69.5	1.91	3.06	40.4	0.72	11.0	0.43	0.30
16	R.S.	36	175	71.0	2.00	3.00	38.2	1.00	11.6	0.43	0.29
17	J.M.	23	200	73.5	2.16	2.85	35.0	0.85	11.3	0.39	0.24
18	B.S.	27	165	71.5	1.95	2.75	37.8	1.00	12.7	0.39	0.29
19	H.M.	30	150	73.0	1.90	2.57	36.5	1.10	13.5	0.39	0.20
20	R.M.	25	155	67.0	1.81	2.43	36.3	0.60	12.9	0.37	0.31
21	W.B.	24	162	69.5	1.90	2.40	32.3	0.90	12.0	0.43	0.31
22	A.K.	27	195	70.5	2.08	2.30	28.5	1.10	11.5	0.32	0.25
23	S.J.	24	155	66.0	1.79	2.11	23.5	1.03	9.9	0.42	0.29
24	L.H.	21	151	66.0	1.77	1.95	37.6	0.60	17.1	0.40	0.32
25	L.P.	32	165	63.0	1.78	1.84	26.3	1.10	13.1	0.37	0.32

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Women											
1	G.L.	28	115	63.5	1.53	3.73	48.8	0.55	10.9	0.61	0.50
2	M.D.	30	140	68.0	1.51	3.15	42.2	0.65	12.3	0.57	0.42
3	J.H.	26	116	66.0	1.58	3.14	44.7	0.65	12.2	0.52	0.37
4	C.W.	20	121	67.5	1.64	3.05	38.9	0.57	10.3	0.57	0.41
5	B.C.	29	110	63.0	1.50	3.00	47.0	0.60	14.0	0.54	0.42
6	O.G.	19	125	64.0	1.60	2.94	46.9	0.45	13.3	0.54	0.38
7	J.W.	26	128	65.5	1.64	2.88	30.8	0.44	8.9	0.51	0.44
8	J.A.	19	137	65.5	1.69	2.87	43.7	0.70	13.5	0.56	0.43
9	L.P.	25	131	65.0	1.64	2.75	42.3	0.60	13.3	0.52	0.42
10	E.M.	30	100	60.0	1.40	2.65	27.6	0.55	8.5	0.51	0.42
11	P.C.	25	130	67.5	1.68	2.61	43.5	0.50	14.3	0.47	0.32
12	M.C.	24	116	64.0	1.56	2.56	33.7	0.60	11.6	0.51	0.38
13	G.S.	24	150	65.5	1.76	2.55	29.7	0.60	9.9	0.50	0.28
14	B.H.	21	136	70.0	1.76	2.53	26.5	0.77	9.2	0.45	0.33
15	M.P.	35	145	66.0	1.74	2.52	42.7	0.80	15.1	0.50	0.39
16	E.S.	19	145	64.5	1.71	2.50	40.8	0.45	13.3	0.48	0.41
17	D.I.	35	155	64.5	1.76	2.27	37.3	0.75	15.0	0.53	0.40
18	E.W.	38	155	67.0	1.81	2.25	31.9	0.70	11.9	0.47	0.40
19	V.V.	27	130	67.0	1.69	2.23	22.6	0.65	8.8	0.55	0.38
20	W.T.	31	177	66.0	1.90	2.13	23.4	1.25	10.3	0.46	0.32
21	L.A.	39	136	61.0	1.60	2.03	34.2	0.53	13.1	0.41	0.34
22	L.B.	23	106	61.0	1.44	2.00	27.6	0.70	11.8	0.45	0.36
23	R.C.	25	126	63.0	1.58	1.83	33.9	0.60	16.1	0.43	0.38
24	R.H.	18	130	65.0	1.64	1.58	24.4	0.50	12.4	0.43	0.31
25	M.B.	26	155	64.0	1.75	1.50	24.2	0.85	14.7	0.34	0.23

TABLE II. DESCRIPTIVE DATA IN PULMONARY GAS DISTRIBUTION STUDIES IN POLIOMYELITIS PATIENTS

RANK	SUBJECT	AGE (YR.)	TIME FROM ONSET (MO.)	WEIGHT (LB.)	HEIGHT (IN.)	B.S.A. (SQ. M.)	PREILLNESS B.S.A. (SQ. M.)	FRC (L.)	CLEARANCE VENTILATION (L.)	TIDAL VOLUME (L.)	CLEARANCE EQUIVALENT	FRC / TLC
Men												
1	H.W.	29	1	150	70.5	1.84	1.92	4.31	36.0	0.68	6.9	0.57
2	S.F.	20	4	115	71.5	1.68	1.88	4.24	52.1	0.96	10.7	0.58
3	J.S.	19	1	159	70.0	1.87	1.87	3.31	43.4	0.70	10.9	0.62
4	M.W.	38	18	127	74.0	1.79	2.01	3.30	53.3	0.56	12.7	0.59
5	E.R.	33	5	140	72.0	1.82	1.90	3.29	33.7	0.59	8.1	0.55
6	J.W.	27	2	157	71.0	1.89	2.03	3.00	44.1	0.79	12.5	0.61
7	A.W.	23	2	175	71.0	1.97	1.97	2.96	19.2	0.64	5.3	0.58
8	D.J.	22	12	110	70.5	1.64	1.84	2.95	38.9	0.86	11.4	0.55
9	M.S.	29	13	120	70.0	1.68	1.91	2.93	114.5	1.17	35.1	0.66
10	G.K.	23	16	115	74.0	1.70	2.17	2.81	23.4	0.52	6.4	0.54
11	J.O.	23	2	168	73.0	1.97	2.13	2.74	30.5	0.55	8.7	0.49
12	F.C.	33	4	155	70.5	1.88	2.10	2.44	33.0	0.72	11.2	0.47
13	C.S.	24	13	107	70.0	1.59	1.84	2.43	16.6	0.69	5.6	0.54
14	J.R.	22	18	118	70.5	1.67	1.87	2.39	35.3	1.36	13.5	0.57
15	T.K.	32	7	148	60.5	1.83	1.92	2.34	27.9	0.72	9.9	0.48
16	R.B.	24	15	135	68.0	1.72	1.80	2.33	25.1	0.49	8.2	0.47
17	H.W.	42	5	128	69.5	1.70	1.92	2.33	36.4	0.58	12.4	0.57
18	C.R.	22	17 (days)	155	71.0	1.87	1.94	2.25	35.1	0.79	13.2	0.50
19	J.K.	16	17 (days)	120	72.0	1.70	1.70	1.94	34.5	0.73	14.9	0.58
20	V.F.	26	8	136	70.0	1.77	1.87	1.76	15.3	0.55	6.8	0.48

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Women												
1	R.B.	26	13	107	66.5	1.54	1.64	2.92	41.7	0.64	11.6	0.68
2	B.S.	23	10	92	65.0	1.42	1.54	2.60	42.6	0.76	13.8	0.62
3	J.W.	26	3	132	67.5	1.71	1.88	2.56	38.5	0.75	12.6	0.65
4	G.A.	27	10	105	65.5	1.51	1.60	2.55	33.9	0.69	11.0	0.45
5	L.K.	33	2	98	61.5	1.39	1.48	2.46	24.6	0.47	7.5	0.53
6	S.M.	34	18	115	62.0	1.50	1.53	2.30	35.2	0.53	11.8	0.50
7	M.M.	33	13	119	67.0	1.61	1.89	2.29	22.3	0.54	7.5	0.52
8	D.P.	27	10	109	66.0	1.56	1.73	2.21	24.9	0.45	8.3	0.46
9	B.L.	20	3	115	64.0	1.53	1.60	2.17	29.1	0.40	9.4	0.52
10	M.D.	23	6	121	64.0	1.58	1.64	1.80	25.9	0.78	12.2	0.46
11	T.E.	26	1	105	64.0	1.47	1.54	1.50	17.1	0.70	9.4	0.47
12	F.S.	20	14	104	64.0	1.48	1.48	1.49	11.2	0.34	4.9	0.56
13	L.A.	31	22	111	62.5	1.51	1.51	1.47	19.7	0.82	11.4	0.48
14	C.B.	19	8	124	63.0	1.57	1.59	1.43	16.5	0.83	9.8	0.47
15	B.C.	33	13	107	65.0	1.52	1.58	1.28	12.8	0.53	7.7	0.44

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TABLE III. PHYSICAL CHARACTERISTICS AND PULMONARY NITROGEN CLEARANCE VALUES OF HEALTHY PERSONS AND POLIOMYELITIS PATIENTS

GROUP	STATISTICAL OBSERVATION	DAYS FROM ONSET	AGE (YR.)	WEIGHT (LB.)	HEIGHT (IN.)	B.S.A. (SQ. M.)	PREILLNESS B.S.A. (SQ. M.)	FRC (L.)	CLEARANCE VENTILATION (L.)	TIDAL VOLUME (L.)	CLEARANCE EQUIVALENT	FRC / TLC	RV / TLC
Healthy males (N = 25)	Range		19–38	130–200	63–73.5	1.71–2.16		1.84–3.75	23.5–67.7	0.47–1.25	8.9–18.1	0.32–0.54	0.20–0.41
	Median		26	162	69.5	1.90		3.11	40.4	0.85	12.2	0.43	0.31
	Mean		27	162	69.5	1.90		3.01	42.4	0.84	12.7	0.44	0.30
	S.D.		4.8	19.7	2.8	0.13		0.57	10.98	0.20	2.25	0.06	0.05
Male polio patients (N = 20)	Range	17–552	16–42	107–175	60.5–74	1.59–1.97	1.70–2.17	1.76–4.31	15.3–114.5	0.49–1.36	5.3–35.1	0.47–0.66	
	Median	156	24	136	70.5	1.78	1.92	2.78	34.8	0.70	10.8	0.56	
	p							0.054	0.012		0.008	0.001	
Healthy females (N = 25)	Range		18–39	100–177	60–70	1.40–1.90		1.50–3.73	22.6–48.8	0.44–1.25	8.5–16.1	0.34–0.61	0.23–0.50
	Median		26	130	65	1.64		2.55	34.2	0.60	12.3	0.51	0.38
	Mean		26	133	65	1.64		2.53	35.6	0.64	12.2	0.49	0.37
	S.D.		5.9	17.8	2.3	0.12		0.52	8.38	0.17	2.16	0.06	0.06
Female polio patients (N = 15)	Range	17–667	19–34	19–132	61.5–67.5	1.39–1.71	1.48–1.89	1.28–2.92	11.2–42.6	0.34–0.83	4.9–13.8	0.44–0.68	
	Median	302	26	109	64	1.52	1.59	2.21	24.9	0.64	9.8	0.50	
	p							0.008	0.004		0.003	0.316	

portions of the lungs. The proportion of the tidal volume required for the ventilation of the anatomic dead space fails to reach the alveoli and is not directly available for alveolar flushing. Nonuniform inflation of lung segments may depend on slight inequalities of the direction and magnitude of enlargement of the boundaries of the thoracic compartment during inspiratory movements and on regional variations of mechanical properties (compliance and airflow resistance) of the lung tissue itself (e.g., in hilar, peripheral, apical, and diaphragmatic areas). Although these factors may be of little functional importance and of small magnitude in the healthy person, they may be greatly altered in pulmonary and thoracic disease.

Theoretically, these two major factors in "mixing efficiency" can in turn be modified by (1) the depth of tidal ventilation, (2) the magnitude of the resting lung volume (FRC) into which the tidal volume is dumped, and (3) the variations in airflow properties of the conducting passages of the lungs at different frequencies of breathing. The depth and frequency of breathing change the clearance equivalent very little when this measurement is made during steady-state breathing in the same posture. The effect of differences in the FRC is offset by the calculation of the clearance equivalent, since the clearance ventilation is referred to a unit volume (1 L.) of the FRC. The effectiveness of airway mixing with a "cone" air wave front versus a square wave front has been identified as a factor in alveolar ventilation when the tidal volume is reduced.[20] Its relationship to the nitrogen elimination process is not known. The contribution of diffusion processes to decreasing alveolar N_2 concentration in the circumstance of breathing of 100 per cent oxygen has been recognized[21] and quantitated.[22]

In spite of the fact that during steady-state breathing some air-bearing portions of the lungs are less uniformly ventilated than others, it is very likely that these areas are not constantly the same. The frequent changes of body position and rate and depth of breathing in the course of ordinary daily activities (sighing, yawning, coughing, sneezing, crying, laughing) seem to offer ample opportunity for periodic maximum and more uniform filling and emptying of practically all the alveoli.

The departure of the clearance equivalent in good health from values that would be obtained with perfect performance can be clearly demonstrated. Assuming an "ideal" alveolar system without dead space and with continuous ventilation, perfect mixing, and a single exponential washout during breathing of 100 per cent oxygen, only 4.4 L. of ventilation would be needed to decrease a 79 per cent beginning N_2 concentration in 1 L. to a 1 per cent ending concentration.*

*The theoretic minimum clearance equivalent can be calculated using the following formulas:

$$C_{EQ\ min} = \frac{\dot{V} \cdot t_{0.01}}{V\left(1 - e^{-\frac{\dot{V}}{V} t_{0.01}}\right)} \quad \text{and} \quad \frac{F_{N_{2_t}}}{F_{N_{2_0}}} = e^{-\frac{\dot{V}}{V}t},$$

where $C_{EQ_{min}}$ is the minimum clearance equivalent, $\dot{V}$ is the alveolar minute ventilation, V is the alveolar volume, $t_{0.01}$ the time required to reach a fractional concentration of 1 per cent nitrogen, $F_{N_{2_0}}$ the fractional concentration of N_2 at the start of the washout (0.79), and $F_{N_{2_t}}$ the fractional concentration of N_2 at time t (0.01).

The difference between this theoretic minimum clearance and the value observed in supine, healthy men during natural breathing of 12.1 L. is equally attributable to anatomic dead space ventilation effects and to real uneven distribution of inspired air among alveoli. This observed difference shows that during breathing of 100 per cent oxygen the nitrogen probably is not equally flushed from all alveoli at the same time (asynchronously) and in the same amount in each breath.

If a correction is made for the ventilation of the anatomic dead space, a pure "alveolar" clearance equivalent can indeed be calculated.* The mean value of this index in healthy persons in the sitting position is approximately 7.25, which is still larger than the theoretic minimum.[13] This additional difference between ideal and actual thus gives some estimate of the unevenness of distribution and mixing at the alveolar level that contributes to the net value of the nitrogen clearance equivalent as determined in this particular study.

Significance of a High Nitrogen Clearance Equivalent.—Individuals with pathologic processes affecting the airway and lung parenchyma ought to present disturbances of the distribution and mixing of the inspired air. Under pathologic circumstances, variations are likely to occur in the anatomic dead space, in regional alveolar anatomy, and in regional "alveolar compliance" and airflow properties. Changes in one or several of these factors might therefore be indicated by measurements of the nitrogen clearance equivalent.

Luft demonstrated that a high clearance equivalent is found in various conditions, especially syndromes with airway obstruction (bronchiolar), such as bronchial asthma and obstructive emphysema, and in diseases producing less compliant lungs, such as pulmonary fibrosis.[6] This finding is considered to be indicative of severe impairment of the mixing and distribution ("ventilatory efficiency") of gases in the lungs.

A high clearance equivalent is believed to reflect a considerable decrease in the size of the airway communication (functional alveolar-bronchiolar junction) of a significant number of air-containing alveoli. Additionally, alveolar volumetric excursions during breathing may be restricted because of decreases in tissue compliance. All of this in turn causes a retardation of alveolar and inspired air mixing and exchange. In this condition, prolonged ventilation is required to flush out the nitrogen contained in such altered lung segments. The existence of a large anatomic dead space in these conditions may also contribute to the prolonged clearance of pulmonary nitrogen. Asynchronous dumping of alveolar nitrogen into expired air from intermittent alveolar trapping may also cause the observed breath-by-breath unevenness of nitrogen elimination. These findings have been substantiated by numerous studies carried out with different methods of evaluation.[20,23-25]

*If the anatomic dead space is accurately measured, the alveolar clearance equivalent (C_{EQ_A}) may be calculated using the following formula (Luft[6]):

$$C_{EQ_A} = \frac{V_E \left(1 - \frac{V_D}{V_T}\right)}{FRC - V_D},$$

in which V_E is the clearance ventilation, V_D the volume of the anatomic dead space, V_T the tidal volume, and FRC the functional residual capacity.

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Significance of a Low Clearance Equivalent.—A clearance equivalent significantly lower than the values observed in good health would indicate that the distribution of inspired air in the pulmonary system is changed toward that observed in an ideal system. Conceivably, this might happen if any or all of the following things are present: (1) the anatomic dead space is smaller than normal, (2) there is a more uniform depth and frequency of breathing, and (3) there is increased "accessibility" of a significantly large number of alveoli. The latter is taken to mean that the proportion of tidal ventilation available to flush out alveoli is greater than ordinarily encountered. This could occur if there is a reduction in the number (but not necessarily size) of ventilated alveoli per unit volume of lung tissue or if there is less restriction to the ingress and exit of flushing gases. This, in turn, may result from anatomic changes of the alveoli and altered mechanical behavior of a large proportion of the lung segments that are being ventilated. Under these circumstances less volume of ventilation would be required to clear out the lung nitrogen per unit volume of aerated tissue.

Although low clearance equivalent values approximate values found with an ideal system, it is questionable whether this can be interpreted as more desirable. It has already been suggested that the FRC acts as a buffer to prevent excessive changes in alveolar gas concentration and composition.[25] If the accessibility of the alveoli to the inspired air is increased and a quick flushing of the alveolar gases takes place, the changes in alveolar composition may be too rapid and perhaps beyond homeostatic physiologic diffusion ranges. Therefore, even though a low clearance equivalent value might be interpreted to indicate greater "ventilatory efficiency" than normal, as we presently express it, we should not presume that this is better for the over-all purposes of external respiration.

Significance of the Low Clearance Equivalent in Poliomyelitis Patients.—Since the majority of the poliomyelitis patients of this study had a clearance equivalent lower than the ones observed in good health, it may be inferred that at least respiratory muscle paralysis and artificial respiration changed the conditions of ventilation. It is impossible to ascertain precisely from this study to what extent this was due to pathologic changes that follow respiratory muscle paralysis or to the artificial respiration being carried on at the time of the test.

It is possible that greater regional variations in the degree of expansion of the alveoli took place in the course of the prolonged artificial respiration to which these patients were subjected. That there are preferential pathways for inflation has been suggested,[27] and this situation could result in overdistention of alveoli in some portions of the lung and underinflation or atelectasis of others. Changes of this type can presumably contribute to the low clearance equivalent we observed.

The results of this study and consideration of the factors affecting the clearance equivalent lead to the following questions:

First, is the volume of the anatomic dead space different in poliomyelitis patients? This lung compartment was not determined; yet we can conclude from these data that the presence of a low clearance equivalent cannot be adequately explained by this alone. In some of the patients the over-all nitrogen clearance equivalent was even lower than the normal values of "alveolar" clearance equivalent.[13] This, in itself, indicates that the flushing of alveolar nitrogen was faster

regardless of a possible maximum diminution in the dead space. If the assumption is made that the alveolar clearance equivalent of the poliomyelitis patients was within healthy ranges, a negative value of dead space would be required to yield the low values of over-all clearance equivalent actually found. This, of course is impossible.

Second, could the maintenance of a constant tidal volume during the washout test have decreased the clearance equivalent? The poliomyelitis patients were studied during tank respirator respiration at constant settings of pressure and rate during the washout. This, indeed, produced greater uniformity of breath-by-breath tidal volume than was observed in the healthy persons' spirometer records. This also cannot solely account for the great reduction in clearance equivalent found in many of the poliomyelitis patients. All of the patients had constant tidal volumes, and yet several of them had normal or even higher than normal clearance equivalents. Besides, we have observed that during natural breathing test periods, individuals with respiratory muscle paralysis still maintain a breath-by-breath constancy of tidal ventilation and frequency. Their clearance equivalent during these brief periods of natural breathing may be much larger than the value obtained when they are studied during artificial respiration even when the tidal volumes are of the same magnitude.[28]

Third, do ventilation levels greater than those observed in basal, steady-state breathing increase the "accessibility" of the alveoli and yield low clearance equivalent values? An answer to this question is pertinent because the patients had volumes of ventilation per minute which usually exceeded those predicted for steady-state breathing.[9] However, the minute volume in the patients did not exceed those of the healthy persons of this study in whom there was slight hyperventilation under test circumstances. Consequently, differences in ventilation are an unlikely explanation for the low clearance equivalents of the contrasted patients. Simple rank order comparison of minute volumes and clearance equivalents of the healthy individuals and of the patients failed to reveal significant correlations. This finding is in agreement with studies of others who did not observe appreciable differences in distribution and mixing of inspired air in healthy persons during breathing at increased rates[19] and during hyperventilation following exercise.[29,30]

Fourth, are large changes in the lung compartments, e.g., resting lung volume (FRC), related to the findings? The over-all magnitude of the FRC of these patients was studied and has no apparent relation to the observed reduced clearance equivalent in rank order comparisons. In a few of the patients, the FRC was normal or even higher than normal. In direct contrast, some of the patients who had clearance equivalents within the normal range also had a marked reduction in FRC. The decreased FRC in patients with respiratory muscle paralysis has been reported by us in a previous communication[3] and is substantiated by the findings of subsequent studies in an enlarged series of poliomyelitis patients. Multiple factors may be incriminated to explain this reduction in the FRC. These include changes in shape and volume of the thoracic compartment that result from respiratory muscle paralysis, constant use of some types of artificial respiration, and mechanical changes in pulmonary and thoracic compliance.[8,31,32]

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The uniformity of the low or normal clearance equivalents obtained in all but one case is markedly different than what would be expected from the FRC/TLC index, which was higher on the average than that of healthy persons. This suggests that it is inadvisable to adopt the FRC/TLC index as a criterion for the establishment of a diagnosis of obstructive emphysema in patients affected with respiratory muscle paralysis.[1]

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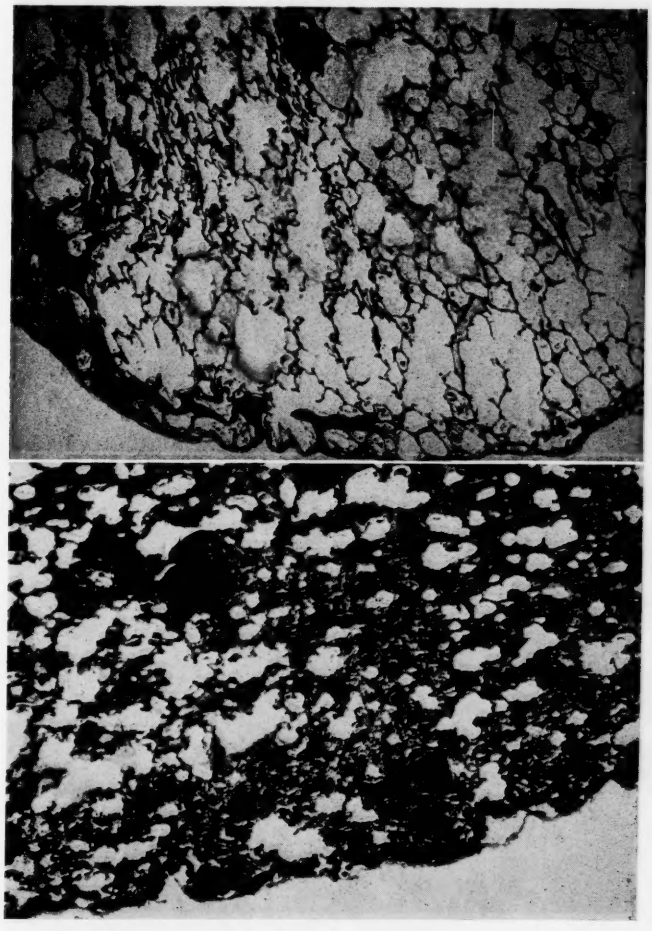
A.



B.

Fig. 2.—Microphotographic reproductions of sections of lung tissue in a poliomyelitis patient. These sections are from different parts of lung tissue which were removed post mortem from the same adult patient. He was a 32-year-old man who had onset of poliomyelitis 2 years prior to death. His vital capacity was 0.50 L., and he used breathing aid (cuirass respirator) constantly. Sections were taken after the lungs were removed from the thoracic cavity. The trachea had been ligated prior to opening of the thorax.

A, The section of the anterior portion of the lung at the pleural surface. Grossly, blebs were visible and the consistency was nonuniform. The alveoli appear overdistended. *B*, A section taken under similar conditions in the posterior part of the same lung. This area was atelectatic on gross examination and had a nonaerated consistency. This section shows marked reduction in the volume of aerated alveoli.

Significance of the Study.—We conclude that the low nitrogen clearance equivalent values observed in some of the poliomyelitis patients were determined largely by an increased ventilatory "accessibility" of a significant number of alveoli. Summated effects of a variety of causes may be equally contributory.

The variability of the values of nitrogen clearance equivalent in the poliomyelitis patients indicates that there is no definite pattern of pathologic alteration of alveolar geometry or of the mechanical characteristics (compliance, resistance to flow) in different areas of the lungs. In some cases one may postulate a condition of preponderance of areas of overventilated, unobstructed alveoli. In other cases these areas may alternate with regions of alveoli of normal size and communication, with areas of partially obstructed alveoli, and, last, with areas of completely collapsed alveoli (i.e., atelectatic). Postmortem pathologic observations in a limited number of cases support this final assumption. (Fig. 20.)

Whether or not these abnormalities of distribution are of significance in gas exchange and pulmonary perfusion cannot be determined from our data and is the subject of future research. On the basis of the relationship between pulmonary blood distribution and lung volume,[33] it may be assumed that in the patients with small lung volumes and limited ventilatory excursions there will be little opportunity for variations in pulmonary arterial pressure. As a result of this, certain capillary areas may remain closed and several alveoli may become underperfused or not perfused at all. This should be reflected in changes of the alveolar dead space. We have planned a longitudinal study of the relationship of these changes to the use of artificial respiration and to the limited ventilatory excursions encountered during prolonged natural breathing in the presence of partial respiratory muscle paralysis (reduced vital capacity).

Studies carried out by use of the lung nitrogen clearance technique in poliomyelitis patients beyond 2 years from the time of onset are reported separately. These studies indicate that, in time, changes in the process of gas distribution may be opposite to those reported here. The findings have been substantiated by serial determinations over a period of years.

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SUMMARY

Lung gas distribution and mixing during artificial respiration were studied in 35 patients with respiratory muscle paralysis caused by poliomyelitis. The onset of their disease had occurred within 2 years before the time of study. The results were contrasted to those obtained during natural breathing in 50 healthy persons of similar ages, sexes, and physical characteristics. In general, but not invariably, the values of clearance equivalent of the patients were lower than those obtained in good health. It is assumed that in these patients some decrease in anatomic dead space and regional changes in the alveoli take place. We postulate from this study that the prevailing pulmonary condition in the early course of artificial respiration and respiratory muscle paralysis is one of a reduced total number of ventilated alveoli that may be larger than normal and have increased "accessibility" to tidal ventilation. These are probably interspersed with small atelectatic areas. This situation may change with time and the extent to which

natural breathing can be resumed. The significance of these findings for pulmonary gas exchange and diffusion is unknown.

The authors express their appreciation to Dr. Richard H. Shepard, who, in reviewing the original manuscript, proposed the equation for the calculation of the "theoretic minimum clearance equivalent."

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A REVIEW OF THE EVIDENCE ON THE RELATIONSHIP BETWEEN SMOKING AND LUNG CANCER

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DURING the past generation, lung cancer has changed in status from an uncommon disease to the one that now represents by far the most common cause of death from cancer of any site in man.

Because most cancers of the lung are widely believed to be of environmental origin—and therefore to offer hope of ultimate prevention—and because reports in the literature on their relationship to the smoking habit are so numerous, this review was compiled to provide a critical examination of the current status of evidence on the subject.

An effort has been made to weigh the evidence for and against the several published interpretations of data presented. The many contributions which have seemed pertinent cannot be justly surveyed. A perusal of the original literature is recommended to help clarify questions which are but incompletely discussed in the succeeding pages.

EPIDEMIOLOGIC EVIDENCE

Twenty-seven reports of new and original data have been published which show that lung cancer patients more frequently have histories of smoking than have persons without lung cancer.[20,50,53,54,92,135,150,157,158,165,175,176,180,201,216,218,220-222,237,238,252,253,258,259,261,265] Two of these studies deal exclusively with women.[92,258] In three follow-up studies on smoking and nonsmoking subjects,[55,56,62,63,101,103] death from lung cancer was found much more frequently among smokers than nonsmokers; in all three the incidence of lung cancer rose as daily cigarette smoking increased. These reports have received wide publicity and deserve separate study. Their greatest contribution was the demonstration that lung cancer accounts for only a fraction of the total excess mortality associated with smoking.

A number of investigators have expressed doubt as to the significance of the association between smoking and lung cancer.[8,9,64,73-75,90,116,117,154,166,167,207,214]

*Administrator for Research on Lung Cancer.

Berkson[8] disagreed with the statement by Hammond and Horn[101] that their "findings prove that there is a definite association between smoking habits and death rates, at least in white men between the ages of 50 and 69." In order to show that the case was not "proved," Berkson set up a model of an experiment showing that if smokers and those seriously ill tended to eliminate themselves from the study, the association could be spurious. He conceded that "at the very least these studies pose a strong presumption that smoking *may* cause cancer and may otherwise be deleterious to health and longevity. My thesis is only that it is unwarranted to conclude . . . that a meaningful association already has been proved beyond doubt . . . ."[8]

In a second article,[9] Berkson questioned "the explanation that the statistical association observed between smoking and lung cancer has a direct causal basis." His reservations, then, were largely confined to the interpretation of the association rather than to its existence. In a third paper,[10] most of Berkson's previous arguments were restated. Since the prospective studies were said to "prove too much," Berkson offers three explanations for consideration: (1) the associations are a spurious statistical phenomenon; (2) the association has a constitutional basis; and (3) smoking speeds up the normal process of aging.

Fisher[73-75] accepts the statistical association between cigarette smoking and lung cancer. His objection to the interpretation that the relationship is causal is based on nonstatistical grounds and will be discussed later.

Comment.—By the end of 1950, in nine retrospective studies[53,150,175,180,201,218,220,252,261] there had been found a positive correlation between smoking and lung cancer. In 1952, Doll and Hill[54] concluded that the association was real. In early 1954, the British Standing Advisory Committee on Cancer and Radiotherapy concluded that "it must be regarded as established that there is a relationship between smoking and cancer of the lung."[226]

Subsequent to Berkson's criticism of the conclusion reached by Hammond and Horn, there were six reports which cast doubt upon the reasonableness of Berkson's suggestion that the correlation between cigarette smoking and lung cancer is not real[39,41,97,123,149,151] (see Appendix A). While Berkson's model may have demonstrated that the case had not been proved for the correlation between smoking and total death rate in Hammond and Horn's initial report on their study,[101] Berkson did not, as the title and discussion of his article implied, present a satisfactory argument against the much stronger association between smoking and lung cancer.

In March of 1957 the Study Group on Smoking and Health, after carefully examining the evidence and paying particular attention to the potential defects in the data discussed by Berkson and others, reported its belief that the evidence for a true association between smoking and lung cancer was satisfactory.[119] More recently, Cornfield and others[41] have discussed the epidemiologic evidence thoroughly. They also concluded that the association between cigarette smoking and lung cancer is satisfactorily established. Hammond[97] has recently answered Berkson's[9] disbelief that cigarette smoking should cause several different diseases statistically associated with it. A fuller discussion of the epidemiologic data will be found under "Estimates of Quantitative Relationships."

EXPERIMENTAL EVIDENCE

In 1953, Wynder, Graham, and Croninger[262] reported that after the shaved backs of 81 CAF_1 mice were painted for prolonged periods with whole cigarette smoke condensate, epidermoid carcinomas developed in 44.4 per cent of the animals. Later, 2 of 89 C57BR and 12 of 86 original Swiss mice developed cancer after similar treatment.[263] In a more recent report,[266] 27 per cent of CAF_1 mice

and 10 per cent of Swiss mice ultimately developed skin cancer after the application of tobacco "tar." All of the Swiss mouse cancers had developed at 15 months and the last cancer on the CAF_1 mice did not appear until the twenty-third month.

There have been several failures[94,192,195-197] in attempts to corroborate the evidence of appreciable carcinogenicity of tobacco smoke condensate as reported by Wynder, Graham, and Croninger.[262,263] Over a period of several years, Passey and others at the Royal Cancer Hospital in London[194-196] were unable to confirm or corroborate Wynder's findings either by application of cigarette smoke condensate to the skin of the mouse, by subcutaneous injection of fresh cigarette smoke condensate into rats, or by instillation of cigarette tar into the left main bronchus of hamsters. Similar negative results after painting mouse skin with cigarette tar were obtained by Orr and associates in the Cancer Research Laboratories of the University of Birmingham.[188]

More recently, Passey[192] has reported development of a subcutaneous sarcoma and five epitheliomas after cigarette tar was painted on the skin of the same strain of Swiss mouse used by Wynder. Because the control as well as the experimental mice frequently got skin ulcerations, however, Passey does not feel that this strain is suitable for such experiments.

Moore and Miller[178] studied the effect of cigarette smoke condensate on the buccal pouch of the hamster and, after applications for periods ranging up to 25 months, noticed occasional hyperplasia of the basal cell layer but no cancers.

When other workers have precisely duplicated the laboratory techniques actually used in the experiments of Graham, Wynder, and Croninger, the results have been in general accord with those reported. Orris and co-workers[189] have discussed some of the reasons for the earlier, unpublished, essentially negative results in their laboratory. The method of preparation of tobacco tar seemed important, since 18 per cent of animals painted with tar prepared in Wynder's laboratory developed skin cancer, while only 8 per cent of the animals tested with the New York University tar did so. Measuring 3,4-benzpyrene and pyrene as possible indices of carcinogenicity, it was found that the Wynder tars producing the largest number of cancers had concentrations of these polycyclic hydrocarbons three to four times as high as those in the other group; the reason for the large chemical difference was not entirely clear.

The carcinogenicity of tobacco tar and its fractions has been demonstrated numerous times on mouse skin[87,179,189,240,262,263] and on the rabbit ear.[84] Its malignancy has been thoroughly established by Croninger and Suntzeff,[44] who found that the skin tumor in CAF_1 mice metastasized in 81 per cent of the animals that received transplants. There are also reports that tobacco tar is carcinogenic to the mouse bladder.[113] That cancer of the bladder in humans is statistically associated with cigarette smoking has been reported[153] and confirmed.[50] In addition, Clemmesen, Lockwood, and Nielsen[31] found a significant excess of smokers among male patients with benign and maligant papilloma of the bladder. By painting the mouse cervix with tobacco tar, Koprowska[122] has induced lesions indistinguishable from early cancer, including some with early invasion.

Della Porta, Kolb, and Shubik[49] reported that acute and chronic tracheobronchitis resulted from instillation into the trachea of hamsters of 200 μg of cigarette smoke condensate twice weekly, but that no cancers were seen after the last of the 21 female test animals died at the end of 55 weeks. The authors did not draw conclusions from the negative results largely because of the low doses of tar used.

Blacklock[13] noted a single oat-cell carcinoma in the lung of one of 8 rats injected with 0.01 mg. of dead tubercle bacilli together with 0.1 ml. of cigarette smoke condensate. Exposure of rats to inhalation of cigarette smoke by Passey and associates[193] did not result in lung cancers, although one of the control animals was found to have a spontaneous lung cancer. Peacock, who designed an ingenious method of exposing lungs of domestic fowls to cigarette smoke in 1955,[197] has not reported any cancers.[198,199]

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Leuchtenberger, Leuchtenberger, and Doolin[146] exposed mice to increasing amounts of cigarette smoke each weekday according to tolerance, up to that of eight cigarettes per day. In this way they were able to study histologic, cytologic, and cytochemical changes. Both inflammatory and proliferative reactions occurred. Bronchitis was the most common finding. The bronchi often showed basal cell hyperplasia with and without atypism after 11 or more days of exposure. Dysplasia and squamous cell metaplasia of the bronchi occurred in one-third of mice subjected to detailed histologic scrutiny after exposure to six to eight cigarettes per day. More than one-half of the mice with bronchitis had foci of epithelial dysplasia in many respects similar to what would be called carcinoma in situ in man.

In 1956, Lasnitzki[143] reported changes of a precancerous nature in tissue cultures of human lung exposed to 3,4-benzpyrene. Subsequently she succeeded in producing a basal cell hyperplasia in an organ culture of human fetal lung by adding cigarette smoke condensate to the medium. She reported that the lesion "resembles that observed after treatment with . . . 3,4-benzpyrene in human foetal lung except that the latter substance only rarely caused squamous metaplasia."[144]

Comment.—To date no frankly invasive epidermoid carcinoma of the lung developing after the application of tobacco smoke or its condensates in animals has been reported in the literature.

Essenberg[69] and Essenberg, Horowitz, and Gaffney[70] reported an increased number of adenocarcinomas in strain A mice after chronic exposure to cigarette smoke. Rockey and coauthors[213] found hyperplasia, transitional metaplasia, and squamous metaplasia after painting the medial surface of the left mainstem bronchus of dogs with tobacco smoke condensate. In a preliminary presentation,[212] Rockey mentioned observing one invasive epidermoid lung cancer after similar painting.

Some studies of the biologic effects of tobacco smoke and its condensates were designed for bioassay and others for determining carcinogenicity of the smoke; still others represented attempts to demonstrate carcinogenicity for a specific organ or tissue. References to such studies are listed in Appendix B by test animal, site, and method, so that the reader may more readily examine the original literature according to his interest in the techniques used.

Unfortunately, the negative results which have been reported by Passey[192] and Passey and associates[194-196] are in the nature of short progress reports to the British Empire Cancer Campaign. Others, however, have presented their work in greater detail.[49,94,146,178,199] The inability of several

workers to induce cancers by exposure of test animals to cigarette smoke or its condensate would be more significant if the reliability of the methods had first been established with the use of known carcinogens at varying doses. There are a great many possible reasons for negative results, and until they are explored, the findings do not weaken the interpretation of the positive results. Failure to establish the susceptibility of the tissue to known carcinogens at varying doses, failure to establish the dose actually delivered to the tissue, and failure to duplicate the conditions of exposure in humans are among the reasons why negative results are not as meaningful as positive ones. Failure to consider the incidence of lesions which might be expected is also a major stumbling block. In pursuing the genetic hazard of ionizing radiation, Carter, Lyon, and Phillips[27] estimate that "at least a million more mice must be scanned before we shall have an estimate of the spermatogonial doubling dose that approaches precision." Similar estimates have not been applied to experimental work on tobacco carcinogenesis.

Experimentally, Kuschner and colleagues,[139] after considerable effort, succeeded in producing epidermoid lung cancer by thread transfixion and pellet implantation using methylcholanthrene and dibenzanthracene (DBA) in rats and mice. It is noteworthy that DBA has been identified in tobacco smoke condensate, although in very low concentrations.[251] Kuschner concluded that the failure of inhalation and intratracheal injection of known carcinogens to produce lung cancers resulted from (1) rapid disappearance of the carcinogen and, consequently, an inadequate dose and (2) the lack of trauma in successful procedures using thread transfixion and pellet implantation. In 1957, Blacklock,[13] after implantation in the lung of a pellet containing 50 per cent 3,4-benzpyrene and 50 per cent cholesterol, found four sarcomas and one epidermoid carcinoma.

Kotin[128] has made the point that attempts to extrapolate from animal experiments to human cancer in a quantitative sense are unwarranted. He takes the position that no tolerable dose of a carcinogen is known. Perhaps the only valid method of comparing dose with response in different species would be to measure the amount of substance in question which actually enters the epithelial cells. Puff frequency, duration, the volume of puff, and the average number of cigarettes smoked per day are superficial indices of dose. That the problem becomes markedly complex has been discussed by Goulden, Kennaway, and Urquhart,[83] who have pointed out the difficulties of distinguishing between summation effects of two weak carcinogens and of cocarcinogenesis.

IDENTIFICATION OF AGENTS INVOLVED IN CARCINOGENESIS

The substances responsible for the carcinogenicity of cigarette smoke condensate have been the subject of considerable research. Of the possible factors involved, three deserve mention: (1) the polycyclic hydrocarbon moiety of the tar, (2) other constituents of smoke that might serve as cofactors or adjuncts in carcinogenesis, and (3) arsenic. Suggestions that cigarette smoke is carcinogenic on the basis of its content of radioactive potassium (K-40) have been made,[181] but effectively disputed by Spiers and Passey.[232] By far the largest amount of attention has been directed toward the polycyclic hydrocarbons.

The purification of fractions of tobacco tar for testing by various bioassay methods has been carried on most extensively by Wright, Bonnet, Lyons, Kosak, and Van Duuren.[16,126,162,189,255,266] In assaying these fractions, Wynder, Neukomm, and Orris[182,189,266] all agree that the major part of the carcinogenic potency for mouse skin is located in the neutral fraction, from which each of the chemists has obtained several chemical subfractions. The neutral fraction on a silica gel column yielded a carbon tetrachloride eluate that produced skin cancers in all 10 mice tested when applied in 10 per cent concentration.[257] This fraction represented 1.7 per cent of the total tar and contained polycyclic hydrocarbons, long chain esters, and paraffins, the major one being hentriacontane according to Wynder.

The carcinogenicity of tobacco smoke condensate is not, however, confined to the neutral fraction. For example, after painting CAF_1 mice with the acidic and with the nicotine-free basic fractions of tobacco tar, Wynder and Wright[266] obtained skin cancers in 7 per cent of the animals in each group.

Cofactors.—Both epidemiologic and experimental approaches have been made to the study of cocarcinogens or adjuncts for carcinogens in tobacco. Epidemiologic data of Stocks and Campbell[238] suggest that smoking and atmospheric pollution do not have a synergistic effect on each other. For example, the lung cancer death rate was found to be high (363 per 100,000) among heavy smokers aged 54 to 74 in rural areas where air pollution is minimal (0.7 μg of 3,4-benzpyrene per 100 c.M.); for the same age and smoking group the rate is only 9 per cent higher (394 per 100,000) in Liverpool, where the average concentration of 3,4-benzpyrene in the air is over ten times as great.

The studies of Gellhorn[78] suggest, but do not establish, cocarcinogenesis. Tobacco tar increased the rate of conversion of benzpyrene-produced papillomas to carcinomas significantly more than croton oil. The effect of tobacco tar on benzpyrene carcinogenesis was more than additive. The mechanism of its action is not clear, however, because the presence of carcinogens in tobacco tar makes alternative hypotheses tenable. In exploring the same thesis, Hamer and Woodhouse,[94] on a smaller scale, noticed more skin papillomas after painting with both 3,4-benzpyrene and tobacco tar than were expected from results with either alone.

The possibility of synergism between beta radiation to the skin and tobacco tar has been examined in preliminary experiments of Suntzeff, Cowdry, and Croninger.[241] Bock and Moore[14] studied the effect of trauma and remote x-irradiation on the development of skin tumors by cigarette smoke condensate. The authors did not find significant differences in tumor production resulting from variation in skin painting technique (shaving or sandpapering skin before painting versus no pretreatment). However, a significantly larger number of skin cancers (seventeen) did appear on animals irradiated before painting than on those only painted (two). Irradiated controls did not develop skin cancers. The effect of irradiation seemed to be systemic.

Arsenic.—Satterlee[217] has favored the thesis that arsenic in cigarette smoke could well act as an important pulmonary carcinogen. Kennaway and his associates[5,47] examined the arsenic content of tobacco and found it to vary from zero in Turkish cigarettes to 106 μg per gram in a commonly used British brand. Monnet and Ruis[178] concluded that amounts of arsenic high enough to be significant were at least not present in Algerian cigarettes.

Varying results have been published regarding the changes in arsenic content of cigarettes over a period of years. Holland and co-workers[111] have claimed that between 1950 and 1957 the arsenic in American cigarettes has risen from approximately 25 to 45 parts As_2O_3 per million. On the other hand, Weber[254] at the Imperial Tobacco Company in England plotted a curve showing that the arsenic of bulk tobacco used in seven leading brands of cigarettes sold in the United Kingdom since 1953 has fallen from 40 to less than 10 parts per million, presumably because arsenic is seldom used now as an insecticide.[254] Guthrie,

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McCants, and Small[88] also published figures showing that the arsenic levels of both cigarettes and flue-cured tobacco have been less than 15 parts As_2O_3 per million since 1953.

Holland and associates[112] have recently described laboratory experiments testing in rabbits the hypothesis that arsenic from cigarette smoke may be a responsible factor in human lung cancer.

Comment.—Evidently, accurate figures are not available on a comparable basis for the arsenic in cigarettes in different countries and different years. The results of Weber might be expected to be more consistently reliable than those of Holland. The latter pooled data from different laboratories and realized that the values may not be representative. Regardless of the recent trends in the arsenic content of cigarettes, it is agreed that there was a gradual increase during the 1930s and 1940s to a level of over 40 parts per million. For cigarettes with 45 μg of As_2O_3, Holland and associates[111] estimated that 4.95 μg would be inhaled in smoking a single cigarette. The Food and Drug Administration permits a maximum of 3 μg of arsenic as As_2O_3 per gram to be present in food.

While arsenic is known to be carcinogenic to human skin,[230] it is not known to have produced cancers in the lung. Goulden, Kennaway, and Urquhart[83] found the average arsenic concentration in the air in eight towns in England to vary from 0.04 to 0.12 μg per cubic meter, depending on the season. The authors estimated that the "standard man" breathes about 20 c.M. of air in 24 hours. Assuming that the air contained 0.07 μg per cubic meter, he would inhale 1.4 μg of arsenic per day. According to Holland's estimates, for a person smoking ten cigarettes a day the actual intake of arsenic by the lungs would be eight times as great per day.

Chemical Analyses of Tobacco Smoke Condensate.—Many chemical studies have been made of tobacco smoke with the purpose of isolating and identifying various compounds rather than attempting to assay purified fractions for biologic activity. In several of these the presence of 3,4-benzpyrene in tobacco smoke has been demonstrated[15,26,36,38,145,163,246,250,266]; in one[138] it was not found. Table I shows its concentration as obtained by several investigators. Wynder, Fritz, and Furth[260] have painted varying amounts of 3,4-benzpyrene on mouse skin and state, "there is conclusive proof that the animal results cannot be solely due to the benzpyrene content of tobacco."[266] In fact, the most potent fraction of the tobacco smoke condensate obtained had only one twenty-fifth of the concentration of 3,4-benzpyrene which would be required to produce the same effect.

TABLE I. 3,4-BENZPYRENE IN SMOKE CONDENSATES OF CIGARETTES

REFERENCE	AS REPORTED	μg PER 100 CIGARETTES
15	2.2 μg per 100 cigarettes	2.2
26	45 μg per 400 cigarettes	11.3
36	4.0 μg per 500 cigarettes	0.8
38	4.0 μg per 500 cigarettes	0.8
138	"Not found in smoke"	0.0
145	6.0 μg per 500 cigarettes	1.2
163	>2 ppm in tar	>8.3*
246	1/30,000,000 oz. per 100 cigarettes	1.0
250	0.5 μg per 100 cigarettes	0.5
266	1-2 ppm in tar	4.2–8.4

*Converted from amount in cigarette tar to estimated amount in cigarettes on basis of 42 Gm. of tar per 1,000 cigarettes.[231]

Kennaway and Lindsey[120] discussed possible exogenous factors etiologically related to lung cancer. They listed ten compounds in tobacco smoke reported to be carcinogenic by Hartwell.[105] They included: arsenious oxide (As_2O_3), 1,2-benzanthracene, 1,12-benzoperylene, 3,4-benzopyrene, chrysene, 5,6-cyclopenteno-1,2-benzanthracene, 6,7-cyclopenteno-1,2-benzanthracene, 1,2-5,6-dibenzanthracene, 3,4-9,10-dibenzopyrene, and 3-methylpyrene. In addition, Lyons and Johnston[163] reported finding 3,4-8,9-dibenzpyrene, which is a well-known carcinogen.[105]

Lyons has since reported the presence in cigarette smoke condensate of 1,2,3,4-dibenzopyrene, of known carcinogenic potency. In the same month, Van Duuren[250] reported the presence of seven aromatic hydrocarbons in cigarette smoke condensate. Later[251] he reported the presence of eighteen aromatic hydrocarbons, four of which had previously been reported as carcinogenic.[105,223] Of the four, two were not mentioned by Kennaway and Lindsey, namely, 1,2-benzpyrene and methyl-3,4-benzpyrene; several others have not been tested for their carcinogenic potency. More recently, Orris and colleagues[189] identified 3,4-benzfluoranthene, which has been reported by Wynder[257] to be carcinogenic to mouse skin.

Since free radicals have been implicated in carcinogenesis by Brues and Barron,[21] it is of interest that Lyons[161] demonstrated both stable and short-lived free radicals in cigarette smoke amounting to 6×10^{15} free electrons per gram. The stable radicals appeared in each of the primary fractions obtained after washing with water, acid, and alkali.

Clemo[33] suggests that the strongly acid cigarette smoke may be the key to the riddle. Thus, curing of tobacco retains the carbohydrates which, when burned, produce an acid smoke. Cigar tobacco is air dried and produces an alkaline smoke. Organic acids in cigarettes such as acetic, propionic, butyric, and the phenols may act both as irritants and as carriers of carcinogens which are soluble in them.

Comment.—From published reports mentioned above it might be concluded that at least nine of the polycyclic hydrocarbons from the neutral fraction of tobacco smoke condensate have been shown to have carcinogenic potency and that an inorganic carcinogen, arsenic, has also been present in significant amounts.[120] The role of several other metallic constituents of tobacco smoke[34] has not been determined.

That the problem of interpreting experimental findings in terms of the causes of human lung cancer is an extremely complex one is borne out by several relationships such as the evidence of carcinogenicity in acidic, basic, and neutral fractions, the fact that carcinogens may inhibit or enhance the action of other carcinogens, and the evidence for "cocarcinogenic" activity of whole tar. The presence of short-lived and stable free radicals complicates it further. The possibility that cigarette smoke acts as an adjunct to carcinogens inhaled from the atmosphere cannot be ruled out solely on the basis that there is epidemiologic evidence of a lack of synergism between cigarette smoking and atmospheric pollution in causing lung cancer.[238] The relatively low incidence of lung cancer in nonsmokers exposed to high concentrations of polycyclic hydrocarbons in the atmosphere does not support the theory that the carcinogens responsible for human lung cancer are concentrated in this fraction of cigarette smoke.

PATHOGENESIS OF LUNG CANCER

Evidence bearing on the pathogenesis of lung cancer will be discussed according to whether the studies deal with inhalation of tobacco smoke, its locali-

zation in the tracheobronchial tree, its penetration into epithelial cells, or the histologic and histochemical changes which may follow. While several links in the chain of events leading to lung cancer are weak or missing, there is a pattern of consistency which justifies discussing the events in sequential order.

Inhalation.—Doll and Hill[53] asked lung cancer and control hospital patients whether they smoked. Of 649 male patients with carcinoma of the lung, 647 said that they did smoke. Of the 649 control patients with diseases other than cancer, 622 were smokers. Another question asked was whether they inhaled. Among the patients with carcinoma of the lung, 61.6 per cent claimed they did inhale; 67.2 per cent of the patients with other diseases admitted inhaling. After correction for sex and age, the difference in inhalation habits between the two hospital groups was not significant.

In contrast, Schwartz and Denoix[221] found the relative risk of acquiring lung cancer to be more than twice as great among those who smoked five cigarettes a day and said they inhaled as among those who smoked five cigarettes without inhaling. The difference in lung cancer risk between those who inhaled and those who did not decreased with increasing use of cigarettes, but it was still appreciable among those who smoked thirty-six cigarettes per day.

More recently, Hammond[99] obtained information from about 70 per cent of roughly 6,000 men to whom questionnaires were sent about their smoking habits with particular attention to inhalation. Depth of inhalation seemed to increase with number of cigarettes smoked. Only 4 per cent of cigarette smokers claimed they did not inhale at all; 30 per cent said they inhaled deeply. In contrast, 54 and 72 per cent of pipe and cigar smokers, respectively, claimed that they did not inhale, only 3.8 and 1.3 admitting to deep inhalation.

Comment.—Fisher[74] has seriously questioned the significance of the association of cigarette smoking with lung cancer largely on the strength of an apparent discrepancy between the hypothesis of a causal relationship and the replies of patients to the question posed by Doll and Hill[53] on habits of inhaling cigarette smoke.

Langer and Fisher[142] determined that the median diameter of cigarette smoke particles is 0.5 μ. This is nearly the diameter of minimum deposition. Below and above a diameter of 0.4 μ there is a tendency for deposition of inhaled particles to increase. Retention increases sharply with slower, deeper breathing. Studies on pulmonary physiology by Dautrebande, Beckmann, and Walkenhorst[48] and Altschuler and associates[1] show that the great majority of cigarette smoke particles present in the inspired air would reach the alveolar spaces because these particles are under 1.2 μ in diameter. The larger particles are deposited higher in the bronchial tree.

Localization.—Hilding[107-109] has described experiments with fresh, postmortem human, cow, and calf lungs on the flow of the mucus blanket which is borne on the cilia of respiratory epithelium. The convergence of the mucus blanket in the mainstem bronchi greatly decreases the surface area on which the mucus flows and enormously increases the local concentration of the nonabsorbed compounds of the smoke condensate. Where there is a break in the normal functioning of ciliated epithelium because of metaplastic changes or the toxic effect of the inhaled deposits, the foreign materials carried by the mucus become arrested and have the opportunity to penetrate through to the basal layers of the epithelium. Hilding tested the effect of cigarette smoke on ciliary activity and

showed that it is highly effective in vitro in stopping ciliary action. He states that nicotine itself in sufficiently high concentrations will stop the action of cilia.[107] Rakieten and others,[203] in a study on mammalian ciliated epithelium, found a roughly linear relationship between nicotine concentration, duration of exposure, and toxicity. Solutions of cigarette smoke were used and therefore results are not easily interpreted in terms of human smoking. However, condensed smoke from twenty cigarettes collected in 25 c.c. of Locke-Ringer's solution slowed and stopped ciliary activity in rat, human, and rabbit respiratory epithelium in 10, 15, and 20 minutes, respectively. Other evidence of decreased effectiveness of cilia in smokers as compared with nonsmokers was reported by Chang.[29] He found that the length of cilia on whole mounts of bronchial epithelium of heavy smokers averaged approximately half that found in nonsmokers. Kotin and Falk[130] found that tobacco smoke interferes with ciliary activity in moving foreign particles.

That convergence of the mucus stream and inhibiton of ciliary action may not be the only factors in localization of foreign material is suggested by the results of Loomis,[159] who demonstrated a bronchoconstricting effect of cigarette smoke.

In another study, Ermala and Holsti[67] found a correlation between the distribution of human lung cancers and the site of localization of tobacco smoke.

Penetration.—That penetration of cells by smoke constituents occurs has been demonstrated by Mellors.[172] Various portions of the smoke can be recognized because of their fluorescent property. When applied to the skin, whole tar, neutral tar, an acidic fraction,[266] and a carbon tetrachloride eluate of the neutral fraction[257] showed an affinity for lipids and keratin in the skin and sebaceous glands. These fractions have been shown to be active in tumor production. The water-soluble fraction, previously shown to be inactive in tumor production on mouse skin,[266] failed to enter the sebaceous glands.[173]

Histologic and Histochemical Changes.—Changes take place in epithelium of mouse bronchi experimentally exposed to tobacco smoke. In experiments of Leuchtenberger, Leuchtenberger, and Doolin,[146] increase in size of the nucleus, in dry mass, and in protein as estimated by tyrosine content occurred early. Changes in desoxyribonucleic acid content of nuclei occurred later. In addition to bronchitis, there was often atypical, proliferative change in the epithelium consistent with dysplasia or carcinoma in situ and "similar to that described for human cigarette smokers by Auerbach et al."

Changes seen by Auerbach and associates[3,4] in human lungs at autopsy include a progressive increase from nonsmokers to heavy smokers for basal-cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ. In these studies the term "carcinoma in situ" was employed for the lesion originally so designated by Black and Ackerman.[12]

Using single whole mounts of the bronchial epithelium, Chang[29] obtained results consistent with those of Auerbach on metaplasia and described also a notable increase in goblet cells of smokers. Cowdry, Suntzeff, and Ide[42,118] were not convinced that the lesions seen in bronchi of smokers represented premalignant changes.

Comment.—The frequency with which Auerbach and associates[3,4] reported carcinoma in situ in sections of the lungs at autopsy has caused some concern among pathologists who are unwilling to pin the cancer label on so common a lesion. Whether or not they are so common, these findings are not peculiar to Auerbach's experience, as evidenced by similar reports from Ryan, McDonald, and Clagett,[215] Hamilton and associates,[95] Valentine,[249] and Chayen, Cunningham, and Winstanley.[30] The implication that carcinoma of the lung may be of multicentric origin is not without support[115]; that multiple primary cancers occur in other sites is not a new finding.[225] It is fair to ask how many of the lesions described by Auerbach as carcinoma in situ do not progress to invasive cancer in a lifetime and whether they can be considered to be a stage in carcinogenesis.

There have been repeated suggestions that chronic inflammation or irritation, as from influenza, bronchitis, or tuberculosis, might be a precursor of the present lung cancer "epidemic" by causing respiratory damage.[205] Baló, Juhász, and Temes[6] have reported the occurrence of alveolar cell proliferations at the borders of pulmonary infarcts and believe they should be regarded as precancerous alterations. Raeburn and Spencer[202] discussed fifteen lung cancers growing in relation to scars, tuberculous lesions, and chronic lung abscesses. They say that eleven histologic types of lung cancer are observed, but columnar-celled tubular cancers are the commonest. Palmer[191] showed a statistically significant association between smoking and both clinical and radiologic evidence of bronchitis. Finke[72] has argued for chronic pulmonary disease as a potentially important factor in lung cancer. Niskanen[183] and Rennie,[206] in extensive appraisal of the problem, discounted metaplasia and its causes per se as precursors of carcinogenesis. Case and Lea[28] studied a group of World War I pensioners who suffered from mustard gas poisoning and found chronic bronchitis in more than 80 per cent. The incidence of lung cancer was increased in patients with chronic bronchitis regardless of whether they had mustard gas poisoning during the war.

Grunze[86] recently reported severe squamous metaplasia and atypical cellular morphologic changes in lungs of patients with bronchiectasis, tuberculosis, and lung abscess. In spite of failure to note cancer associated with these lesions, he believes that they may be a predisposing factor in some cases of epidermoid carcinoma.

More research is needed before pathologists will agree on the significance of the findings of Auerbach or of scars and acute and chronic infections in pulmonary carcinogenesis.

FACTORS OTHER THAN CIGARETTE SMOKING

Numerous suggestions have been made that factors other than cigarette smoking play an important or major role in human pulmonary carcinogenesis. These factors include some which are associated with lung cancer and others on which evidence is either experimental, hypothetic, or based on the pathologic condition. The factors can also be classified according to whether they are associated with occupational or residential exposures, with personal habits or disease history, or with constitutional or hereditary factors. It is not the purpose of this article to review the evidence pertaining to each, but a few deserve mention. If the human populations studied for statistical association between smoking and lung cancer are self-selected, that is, if the people smoke because of some second characteristic associated with lung cancer, the cause-effect hypothesis might not stand up.

Matarazzo and Saslow[170] have reviewed the literature on psychologic, personal, and social characteristics differentiating smokers from nonsmokers. Although twenty-six differences are listed, they narrow down to certain behavioral characteristics (e.g., coffee drinking), personality traits (e.g., Taylor Anxiety Score), and physiologic traits (e.g., dark adaptation), in addition to vital data such as age, sex, and marital status. Five characteristics were listed as not differentiating smokers from nonsmokers, but it is unlikely that a statistically

significant difference could not be obtained with sufficiently large samples for any of them—race, socioeconomic status, education (highest grade attained), intelligence quotient, and effects on mental and motor functioning.

Epidemiologic Evidence.—Perhaps the most thorough retrospective search for characteristics associated with lung cancer was that of Denoix, Schwartz, and Anguera[51] who studied 602 cases of bronchogenic cancer. They examined 160 criteria falling in the categories of social environment, occupation, place of residence, previous hereditary and pathologic factors, nutrition, and smoking habits. Of the 160 criteria, eleven were significantly associated with bronchogenic carcinoma. Among the eleven, the consumption of cigarettes was by far the most strongly associated. The others included history of occupation in glass industry, hairiness of the second phalanges of the fingers, previous chronic bronchitis, drinking of *apéritifs*, coffee drinking, eating cooked snails and oysters, eating shellfish, poor state of teeth, and history of exposure to war gas.

The authors found that chronic bronchitis and poor state of teeth multiplied the risk of bronchogenic cancer largely in average or heavy smokers. War gas multiplied the risk of bronchogenic carcinoma even apart from the use of cigarettes. None of the other characteristics could be compared in importance, from the etiological point of view, with the consumption of cigarettes, not only because some of the criteria are secondarily associated with smoking cigarettes, but because they multiply the risk to a much smaller degree. Whereas some of the criteria only multiply the risk by approximately twofold, the risk is increased tenfold for the average smoker and by thirty to forty for the heavy smoker.

A well-designed study highly pertinent to the self-selection hypothesis was carried out by Lilienfeld.[152] In an epidemiologic study on a systematic sample of the noninstitutionalized population of Buffalo and Kenmore, New York, he found the group of smokers (matched for age, sex, race, and social status with nonsmokers) to be significantly more neurotic than nonsmokers. The term "neurotic" was used in the sense defined by Stouffer and associates.[239] However, the degree of difference was not sufficient to explain the tenfold excess of lung cancer mortality for cigarette smokers as compared with nonsmokers ". . . and therefore, would not influence the derivation of a casual inference from this association."

Another presumably secondary or noncausal association was uncovered by Stocks.[237] He has shown that a history of beer drinking by men is correlated positively with lung cancer. However, he believes the association is secondary to that between beer drinking and cigarette smoking.

Diehl[52] showed a statistically significant difference among smoking and nonsmoking college students in the lability of the cardiovascular system as measured by the Schneider cardiovascular physical fitness test.[219] No other physiologic measurements showed a significant difference.

A different kind of lability was observed in cigarette-smoking members of the Harvard Grant Study. Heath[106] got the impression from results of follow-up studies of 258 Harvard men that the group of smokers contains more of the men who are energetic and perhaps less stable. Of the many variables tested, two showed a statistically significant difference between smokers and nonsmokers.

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The nonsmokers were characterized more often by a "bland affect" and "inarticulateness." No data were given as to whether the differences found between nonsmokers and chronic smokers are inherent or acquired.

In another report from the Harvard Grant Study, McArthur, Waldron, and Dickinson[164] found that whether a man smokes or not "seems to be determined by whether or not he has been oriented to the habit as a result of his social milieu." The ability to stop smoking and the amount smoked are more closely related to the personality structure of the individual. Also, the greater the "psychoanalytic orality" factor, the lower the ability to stop smoking.

Fisher[73,75] found that identical twins resemble each other more closely than fraternal twins in smoking habits; he has implied that the habit of smoking is therefore linked to heredity. Differences in lung cancer incidence between smokers and nonsmokers who were not drawn from populations of identical genotype might, therefore, be explained on a genetic basis. Friberg and co-workers[77] confirmed the finding that there is more concordance of identical twins on smoking habits than of fraternal twins but pointed out that it may be because identical twins have a more uniform environment than fraternal twins. Edwards, McKeown, and Whitfield[65] have made an attempt to test Fisher's hypothesis that smokers differ genetically from nonsmokers by looking among smokers for increased frequency of diseases which could not reasonably be expected to result from smoking. Of the eight most common diseases in the population studied, three were related to smoking habits. Peptic ulcer and bronchitis occurred more commonly and hypertension less commonly in smokers than nonsmokers. The association of peptic ulcer and bronchitis with smoking is consistent with clinical experience. That the negative correlation with hypertension was causal is suggested by the fact that blood pressures in men who had given up smoking were approximately the same as in those who had never smoked.

Clemmesen and Nielsen[32] studied the social distribution of cancer in Copenhagen as measured by range of house rent. Data on incidence of cancer were collected by the Danish Cancer Registry. Lung cancer among males increased from 66 per cent of the expected value among the highest rental group to 116 per cent among the lowest rental group. A similar trend occurred for cancer of the uterine cervix. No index of smoking behavior or atmospheric pollution was reported. More recently Cohart[35] divided New Haven into three regions—"well-to-do," "middle class," and "poor"—and also found an inverse relationship between economic status and incidence of lung cancer. It was present for both men and women. Lung cancer incidence was 40 per cent greater among the poor.

Mills and Porter[176] have carried out research designed to examine both atmospheric pollution (as reflected in place of residence) and smoking habits for their relative association with lung cancer. They also included a study of annual miles driven by automobile. While they found significant associations between lung cancer and (1) smoking history, (2) residence in the Basin district of Cincinnati, and (3) annual automobile mileages in excess of 12,000 miles, the data were not adequate to attach quantitative significance to the part played by each factor.

Haenszel and Shimkin[91] estimated that ratios of urban to rural lung cancer death rates could be in error by as much as 5 to 10 per cent by reason of relative overstatement of the urban lung cancer rate through incorrect residence information. Definitive studies showing the tendency of ill patients to migrate to urban areas have not been published. Still another potential source of error in these estimates is the lack of lifetime residential histories in existing data. Another factor introducing a potential source of error is the possibility of better diagnostic facilities in urban than in rural areas tending to distort the mortality data in favor of urban deaths. A study of the basis of diagnosis of primary lung cancer in urban and rural sections of Norway is of interest in this connection.[200] Whereas 88 per cent of the urban diagnoses were histologically established, the percentage in rural areas so established was lower, 76.8 per cent. It should be pointed out that this difference would not nearly account for the difference in lung cancer incidence between urban and rural areas. This problem has been discussed by Haenszel and Shimkin.[91]

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Wynder and Lemon[265] have presented data suggesting that atmospheric pollution has not played a leading role in the causation of lung cancer in Los Angeles, noted for its smog. In its reputation for atmospheric pollution, the counterpart of Los Angeles in England is Liverpool. However, its total soot fall is much greater. Stocks and Campbell[238] found the lung cancer death rate reported among nonsmokers of Liverpool to be nine times as great as that reported for rural sections of Wales. When heavy smokers were compared, however, the urban-rural differences almost entirely disappeared. They state that "the absolute urban excess (in lung cancer death rate) is much the same in each smoking group, suggesting that an 'urban' factor is added to the effects of smoking." Even in the highly air-polluted city of Liverpool they estimate that half of the lung cancers are associated with smoking and that another three-eighths are due to a factor only slightly present in the rural areas.

In a later study,[237] using different populations, Stocks found the lung cancer mortality rates in nonsmokers to have an urban-rural ratio of only 2.3, instead of 9.0 as previously found.[238] The cause of this difference is not clear. In spite of a tenfold excess of other polycyclic hydrocarbons and trace metals, including arsenic, in Liverpool over rural Wales, the lung cancer death rate of heavy smokers was not significantly higher in those who lived in Liverpool than in those of rural sections of Wales. If it is assumed that the bronchial mucosa is actually exposed to these pollutants and that one or more of them are responsible for lung cancer, it is surprising that the dose-response relationship is so poor.

The variation in lung cancer incidence between countries has been used as an argument against the smoking hypothesis. If these differences are explainable on the basis of cigarette consumption characteristics, the argument would be weakened. The lung cancer death rate in England and Wales is about 2.1 times that of the United States[98] although the total cigarette consumption is about the same. Of the many possible explanations for this difference, several deserve mention. Hammond, in examining the problem, showed on the basis of certain assumptions that the greater urban-rural differential in lung cancer death rates reported in England[238] and the greater degree of urbanization could account for

about half of the difference. In England there is also a significant excess of the percentage of smokers in the age group most susceptible to lung cancer; 52.6 per cent over 60 years of age in the United Kingdom were smokers compared with 29.2 per cent of those over age 65 in the United States. On the other hand, a compensating factor may be the higher proportion of heavy smokers in the United States than in the United Kingdom. In addition to the number of cigarettes smoked per day by susceptible individuals, other measures of the amount of exposure to smoke are factors in determining dose. Although no significant difference in depth of inhalation seems to exist, there is evidence that the length of the unsmoked cigarette butt is shorter in the United Kingdom than in the United States. Hammond[98] found butts to average 30.9 mm. in this country and subsequently Doll and associates[57] found them to average 18.7 mm. in England and Wales. Although the length of cigarette butts collected in the Netherlands (19.7 mm.)[98] was nearly the same as in the United Kingdom, the lung cancer rate there is lower (1.36 times that of the United States) as compared with the United Kingdom (2.1). Another potentially important factor may be the composition of the cigarettes and consequently of the smoke in different countries. British manufacturers are forbidden to use additives other than water, whereas they are used freely in this country.

Experimental Evidence.—The presence of carcinogens in atmospheric pollutants and their capacity to produce skin cancer in animals has been taken by Kotin[127] and Kotin and Falk[132] as evidence that they play an important causative role in human lung cancer. By exposing mice to an atmosphere of ozonized gasoline, Kotin and his colleagues were able to induce an increased number of lung tumors in strain A animals[131,133] and marked epithelial hyperplasia in the C57B1 strain.

Comment.—The study of Denoix, Schwartz, and Anguera[51] seems to substantiate and add to the evidence that cigarette smoking is by far the characteristic most strongly associated with lung cancer. It is of interest that place of residence is not listed as one of the criteria which are positively correlated with lung cancer. Among several other possibilities this may reflect a difference in the distribution of atmospheric pollutants in France.

It is also of interest that the index Mills and Porter used for atmospheric pollution is related to those used by Clemmesen and Nielsen and by Cohart as an index of social or economic status. All three used residential data, Clemmesen and Nielsen relying on range of house rent, the others on location of residence. Many factors, including nutritional history as well as air pollution and social status, are related to data on residence. Because of the tenfold excess of lung cancer in smokers over nonsmokers, small differences in the percentage of smokers, number of cigarettes smoked, depth of inhalation, and number of puffs per cigarette in different populations could easily influence the incidence of lung cancer. Indeed, Edwards, McKeown, and Whitfield[65] found that in England about one in two unskilled workers (social class V) were cigarette smokers, as compared with one in three of professional people (social classes I and II). This is not in accord with the listing by Matarazzo and Saslow[170] of socioeconomic status as a nondifferentiating characteristic of smokers.

The hypothesis proposed by Fisher[73-75] and perhaps implied by Heath[106] is that a genetic difference between smokers and nonsmokers is responsible for the tenfold difference between the incidence of lung cancer in the two groups. It would be surprising indeed if hereditary factors did not play some role, along with environmental factors, in the acquisition and retention of any habit such as smoking. It is a greater step to suggest that the same hereditary factors involved in the acquisition of the smoking habit play an important etiological role in lung cancer. The

argument posed by Fisher would be much stronger if it could be demonstrated that both smoking and nonsmoking members of pairs of identical twins had the same incidence of lung cancer. It would also be more plausible if he could suggest (1) how lung cancer can be genetically linked and show such a steep increase in incidence over the past 50 years, (2) how it could have been acquired selectively by men more rapidly than by women, (3) how epidermoid carcinoma, but not adenocarcinoma, can be linked to a genetic factor, and (4) on what genetic basis lung cancer is correlated not only with the presence or absence of the smoking habit, but also with the degree of smoking. Fisher's hypothesis that epidermoid lung cancer may not be of environmental origin has not been supported by evidence but has been referred to sympathetically by Little.[155,156]

ESTIMATES OF QUANTITATIVE RELATIONSHIPS

If smoking plays a causative role in lung cancer, the question of the magnitude of its contribution to the total incidence is raised. The fact that no true cross section of the country has been studied makes it difficult to estimate the percentage of lung cancer cases that are associated with smoking. Cutler,[45] Cutler and Loveland,[46] Cornfield,[40] and Levin[147,148] have reviewed the risk of death from lung cancer among smokers and nonsmokers as derived from retrospective studies and found a wide variation. From 56 to 92 per cent of the cases have been attributed to smoking.[147]

Although no single study has been designed to show what portion of the national lung cancer mortality is related to smoking habits, a full discussion of such evidence that is available seems indicated. Aside from the retrospective approach, semiquantitative evaluation of the problem can be aided by discussion of five sources of data: errors in certification of cause of death, quantitative evidence for alternative etiological factors, generalization of lung cancer death rates from those of selected populations, ratio of lung cancers of environmental origin to those of idiopathic origin, and follow-up studies.

Errors in Certification of Cause of Death.—Rigdon[207] and Rigdon and Kirchoff[208-210] have questioned the validity of the increase in lung cancer in the last several decades. Rigdon believes the increase is a result of improved diagnostic techniques and facilities and is more apparent than real.

Several studies have been made of the accuracy of death certificate diagnoses. Swartout and Webster,[243] at Los Angeles County General Hospital during the years 1933 through 1937, found that 28 per cent of 99 clinical diagnoses of cancer of the respiratory system represented overdiagnosis. Koletsky,[121] on the other hand, found that 18 per cent of lung cancer cases seen at autopsy in Cleveland City Hospital between 1927 and 1937 had been missed clinically.

In 1954, Dorn[60] considered the arguments that the increase in lung cancer might not be real and concluded that "the major part of the increase in males represents a real increase in the probability of developing cancer of the lung . . . ." In 1955, Gilliam[82] made careful estimates of the possible effects of false-negative reports resulting from the faulty certification of death on the reported twenty-six–fold increase in lung cancer between 1914 and 1950. Earlier in the century, many cases of lung cancer could have been mistaken for tuberculosis. He concluded that it would be unreasonable to deny the existence of any increase of lung cancer mortality solely because of the influence of such an error. The true increase in lung cancer during the interval, he thought, might be as little as fourfold in

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males and only 30 per cent in females, on the assumption that 2 per cent of cases reported as nonmalignant chest disease were in fact lung cancer. He made no estimates of changes in overdiagnoses of lung cancer. This problem was studied by Bonser and Thomas[18] who examined clinical and autopsy records of the same group of cases recorded as lung cancer for false-positive diagnoses. Agreement between death certificate and clinical diagnosis was 96.5 per cent. Of 999 certificates, 35 (3.5 per cent) proved on autopsy not to have been from cases of primary lung cancer.

Spain[231] has collected additional data on the relative incidence of different histologic types of lung cancer found at autopsy over a 44-year span at Columbia-Presbyterian Medical Center. The percentage of total autopsies on men in which diagnosis was pulmonary adenocarcinoma was 0.86 during the interval 1912 through 1941 and 1.16 from 1942 through 1956. In contrast, the percentage of undifferentiated and squamous cell lung cancers increased much more over the same period. During the earlier interval, 2.12 per cent of the 3,014 autopsies on men led to diagnosis of undifferentiated and squamous cell bronchogenic carcinomas,while in the later period the percentage has doubled. The numbers are small, but a striking increase of the same type was found in autopsies on women. The data confirm a previous report published by O'Neal, Lee, and Edwards,[187] who found no evidence that faulty clinical diagnosis of lung cancer could account for the rising incidence as determined from vital statistics.

Quantitative Evidence for Alternative Etiological Factors.—The age-adjusted mortality rate for primary cancer of the lung and trachea among men in nonmetropolitan counties in the United States is recorded as 5.8 cases per 100,000, or 50 per cent less than the rate of 11.5 recorded in counties containing central cities (50,000 or more population).[168] By comparison, Hammond and Horn[103] found the age-adjusted rural lung cancer rate for men aged 50 to 69 to be 37 per cent lower than in cities with more than 50,000 population. After standardizing for smoking habits they found the rural rate to be 25 per cent lower than the large city rate. It is possible to make the tenuous assumption that the same standardization for smoking habits as existed among the rates selected for the Hammond-Horn data would apply for the lung cancer rates of the 163 metropolitan areas used in the Public Health Service data. If this is done, the lung cancer mortality rate, after standardization for both age and smoking habits, would be 34 per cent rather than 50 per cent lower in rural communities than in cities of 50,000 and above as recorded by the Public Health Service.[168] The total population of the United States is distributed in such a way that urbanization might be expected to account for less than 15 per cent of the lung cancer deaths of men between 50 and 70.

Generalization of Lung Cancer Death Rates From Those of Selected Populations.—Haenszel and Shimkin[91] tested the hypothesis that variations in lung cancer rates in the country at large could be explained on the basis of smoking. The expected lung cancer rates for a probability sample of the nation based on results of retrospective and prospective studies of lung cancer by smoking category in selected populations were calculated and compared with the observed lung

TABLE II. DISTRIBUTION OF SELECTED SERIES OF REPORTED LUNG CANCERS BY SEX AND HISTOLOGIC TYPE*

AUTHOR	REFERENCE	COUNTRY	NUMBER OF TYPE I† CANCERS			NUMBER OF TYPE II† CANCERS			TOTAL CASES			PERCENTAGE TYPE I CANCERS		
			M	F	COMBINED	M	F	COMBINED	M	F	COMBINED	M	F	COMBINED
Bignall and Moon	11	England	361	32	393	51	9	60	412	41	453	88	78	87
Boucot and Sokoloff	19	United States			78			16			94			83
Doll, Hill, and Kreyberg	58	England	832	48	880	40	13	33	872	61	933	95	79	94
Gibbon, Templeton, and Nealon	79	United States			135‡			10§			145			93
Gifford and Waddington	80	England	287‖	25‖	312	31	4	35	318	29	347	90	86	90
Kreyberg	136	Norway	162	8	170	28	20	48	190	28	218	85	29	78
Kreyberg	137	Norway	172	4	176	30	29	59	202	33	235	85	12	75
Mason	169	England	662	51	713	60	13	73	722	64	786	92	80	91
Ochsner, Ray, and Acree	185	United States	344	26	370	60	27	87	404	53	457	85	49	81
Ochsner and coauthors	186	United States			387			75			462			84
Overholt and Bougas	190	United States			392			139			531			74
Ryan, McDonald, and Clagett	215	United States	85	1	86	38	11	49	123	12	135	69	8	64
Steele	236	United States			180‖			48			228			79
Totals			2905	195	4272	338	126	752	3243	321	5024			
Weighted means												90	61	85

*Data do not include cases of unverified type.
†Type I: squamous, large and small cell types; type II: adenocarcinoma and bronchiolar carcinoma.
‡Epidermoid and anaplastic.
§Adenocarcinoma and alveolar cell carcinoma.
‖ Includes "undifferentiated."

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cancer incidence in the country. In this way, any discrepancy between the actual incidence and that expected on the basis of the smoking hypothesis could be observed.

Shimkin and Haenszel pointed out that the degree of association of smoking with lung cancer as reported by Cutler and Loveland[46] in estimates based on retrospective studies agrees well with that found by Hammond and Horn.[101] Whereas the incidence of lung cancer mortality in men who smoke more than one pack of cigarettes a day is thirteen to fourteen times that of nonsmokers, Haenszel and Shimkin showed that the age-adjusted mortality rate for lung cancer in men in the whole United States was only 1.85 times as high in urban as in rural areas. For women the ratio was only 1.31.

Ratio of Lung Cancers of Environmental Origin to Those of Idiopathic Origin.—Since several histologic types of lung cancer are recognized, separation of those of environmental origin from those of idiopathic origin should give an indication of the maximum proportion which could be caused by smoking. Kreyberg[136] has presented evidence that adenocarcinoma and bronchiolar (alveolar cell) carcinomas are etiologically distinct from a group consisting of squamous, large and small cell (including oat-cell) types.

Without knowledge of clinical or smoking history, Kreyberg separated slides provided by Doll and Hill into two histologic types which showed a strong correlation with smoking history. Type I, consisting of the squamous and anaplastic types, occurred much more frequently in smokers than in nonsmokers.[58]

Hammond and Horn found only 3.4 cases of well-established carcinomas of the lung (other than adenocarcinomas) per 100,000 man-years in nonsmokers as compared with 78.6 per 100,000 man-years in cigarette smokers.[103] On the other hand, they found the difference in the incidence of adenocarcinomas between smokers and nonsmokers to be almost negligible. Sommers[229] has also published data supporting Kreyberg's thesis. He estimated that 90 per cent of the men with epidermoid carcinoma as opposed to adenocarcinoma of the lung had histories of chronic exposure to suspected carcinogens. While endocrine abnormalities were reported to be uncommon in these cases, in Sommers' experience they were prominent in both men and women with adenocarcinoma of the lung.

Table II shows the percentage of lung cancers, observed by different authors, which fall in Kreyberg's type I classification (squamous, large and small cell types) as compared with those of type II (adenocarcinomas and bronchiolar carcinomas). It is seen that type I tumors range between 64 and 94 per cent of the total cases. While some of the differences among the various reports may be attributed to variations in definitions of a given pathologic entity, and others may be explained by unintentional selection, some of the difference may be real. Of 2,052 lung cancers reported in the United States, 79 per cent belonged in Kreyberg's type I classification. The higher percentage of type I tumors reported in England[11,58,80,169] is consistent with the evidence that the higher incidence of lung cancers in the British Isles has been of environmental origin.

Doll, Hill, and Kreyberg,[58] on the basis of their data, calculated that the relative risk of developing type I as compared with type II cancers increases

from 1 to 1 among nonsmokers to 25 to 1 for heavy smokers. At the same time an increased risk of developing adenocarcinomas according to smoking habits was almost nonexistent. There were only two type I cancers among nonsmokers as compared with 829 among smokers.

Follow-up Studies.—Hammond and Horn,[103] Doll and Hill,[56] and Dorn[62] found the ratio of lung cancer mortality of cigarette smokers to nonsmokers to be 10.7, 9.0, and 9.85 to 1, respectively. In the heaviest smoking category (smokers of two-plus packs a day), Hammond and Horn found the lung cancer death rate for well-established cases of lung cancer, exclusive of adenocarcinoma, to be 217 per 100,000 man-years. Only 4 cases were found among nonsmokers, the death rate being 3.4 per 100,000 man-years.

In the follow-up study of Doll and Hill,[56] a single case of lung cancer was found among nonsmokers during a total of 25,250 man-years studied. None were observed during 24,394 man-years studied among men up to 75 years of age. Hammond and Horn[103] found in their follow-up study an age-standardized lung cancer death rate of 12.8 per 100,000 man-years among nonsmokers as compared with 264.2 among smokers of more than two packs a day. They found occasional smokers to have a rate between 1.5 and 2.9 times that of the nonsmokers. In his follow-up study on 249,000 veterans, Dorn reported 10 deaths among persons with lung cancer out of a total of 89,774 person-years of nonsmokers, giving a crude rate of 11 per 100,000. Agreement with the Hammond-Horn age-standardized rate of 12.8 is good, considering the small number of cases found. A rate for nonsmokers cannot be estimated reliably for the Doll-Hill study, but the single case found suggests that in the absence of cigarette smoking, other factors such as atmospheric pollution are not playing a very significant part.

Comment.—From the above discussions, the meager evidence suggests that in the era before the current widespread interest in lung cancer the net error in certification of causes of death might have been in the direction of clinical *over*diagnosis rather than of underdiagnosis as postulated by Gilliam.[82] The results of two clinicopathologic studies covering several decades of records have shown that errors in certification of cause of death did not account for the large increase in lung cancer mortality reported. Regardless of the accuracy and rate of increase over the last half century, however, it is agreed by authors of three follow-up studies that lung cancer risk among smokers now is ten times greater than that of nonsmokers.

The close agreement of the three prospective studies showing that lung cancer among nonsmokers is approximately 10 per cent as frequent as in persons who regularly smoke only cigarettes is noteworthy. The scarcity of cases of epidermoid lung cancer among the nonsmoking population makes a study of their etiology especially difficult. According to estimates of Levin,[147] two retrospective studies[58,261] would suggest that 91.0 and 92.5 per cent of all lung cancers are attributable to smoking. However, it is seen in Table II that Kreyberg's type I lung cancers alone seem to account, in men, for about 90 per cent of all primary lung cancers. Assuming that type II lung cancers are not of environmental origin, no cases would be left to attribute to atmospheric pollutants or occupational hazards. That the estimates of 91.0 and 92.5 are high is indicated by the lower values estimated from two other studies[20,147] as well as by the fact that adenocarcinomas and bronchiolar carcinomas account on the average for about 15 per cent of all cancers.

The evidence that atmospheric pollution plays a highly significant role in the etiology of lung cancer is meager. It might be expected that a maximum effect would be found in a city with the maximum amount of pollution. Liverpool was selected by Stocks and Campbell because of its high degree of pollution. Nevertheless, they are of the opinion that only three-eighths of lung cancers in Liverpool are associated with urbanization.

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While Haenszel and Shimkin[91] did not attempt to quantify the relative contributions of cigarette smoking and urban residence, the distribution of observed lung cancer mortality rates between urban and rural areas of the United States shows only a modest urban excess over that expected on the basis of the hypothesis that cigarette smoking was the only factor involved.

RESEARCH INTO PREVENTIVE MEASURES

Before lung cancer can be brought under control, it is not only important to discover the causes—it is also essential to learn how to remove those causes in an acceptable way. Three major alternatives referable to smoking have been suggested. They include abolition of the smoking habit, modification of cigarettes to diminish the carcinogenic substances in their smoke, and substitution of an acceptable habit providing most, if not all, the pleasure of smoking.

In regard to the abolition of the smoking habit and its implications for prevention of lung cancer, evidence that cessation of smoking by chronic smokers has resulted in a decreased risk of lung cancer has been presented by Doll and Hill[56] and Hammond and Horn.[103] There are no reports showing how the majority of smokers in a given population can be persuaded to give up smoking, either by education or propaganda. In a study on exsmokers, Hammond and Percy[104] found that a very small percentage of cigarette smokers had given up the habit "consciously and admittedly because of reports linking cigarette smoking to lung cancer and other serious diseases." Similar findings were observed by Nørgaard[184] in a survey of tobacco consumption in Denmark. As of early 1954 it was determined that 4 per cent of smokers had changed their smoking habits after an "exhaustive debate" in all the newspapers in the country about smoking and lung cancer during the previous several months. Only 0.5 per cent had stopped smoking completely. Adequate data are not available on the percentage of smokers who can be led to give up smoking on the basis of its effect on health. However, in Italy 45 per cent of the smokers over the age of 16 questioned in a survey said they felt smoking was a "necessity."[247]

Among physicians in Massachusetts, Snegireff and Lombard[228] found an increase in nonsmokers from 34.1 per cent in 1954 to 44.5 per cent in 1959. Only 38.5 per cent were cigarette smokers in 1959.

Another means of eliminating the smoking habit would be to educate young people not to take up the habit. Horn and colleagues,[114] in a study of smoking among high school students, discovered some of the characteristics associated with those who take up smoking. Of the boys in senior classes in Portland, Oregon, high schools, 35 per cent were regular smokers; 19 per cent had never smoked. Among the girls, 26 per cent were regular smokers and 32 per cent had never smoked. Others had experimented, smoked occasionally, or had given up smoking. Smokers in high schools tend to have parents who smoke, to be relatively inactive in extracurricular activities, not to take a college preparatory course, and to be older than their classmates.

Wynder[256] listed three possible methods of modifying the cigarette to help reduce the lung cancer risk: effective filtration, removal of precursors, and modification of the pyrolytic process. His results on mouse skin showed that reduction of the number of applications of tar by one-third (two paintings instead of three

per week) reduced skin cancers by 85 per cent. In other experiments, however, a 34 per cent reduction of *concentration* of tar in the solution applied three times per week reduced the number of skin cancers by only 20 per cent.[264]

Many organic substances, when pyrolyzed, will give rise to polycyclic hydrocarbons.[140,244,245] A decrease in polycyclic hydrocarbons of tobacco smoke noted by Campbell and Lindsey[24] after pre-extraction of the tobacco with cyclohexane was real, but not large. It was concluded that most of the hydrocarbons are formed during pyrolysis. Bonnet and Neukomm[17] have also discussed methods of modifying tobacco smoke carcinogens. They state that treatments with mineral or organic substances have a bad effect on the taste of the smoke, that pre-extraction reduces aliphatic hydrocarbons by 70 to 80 per cent, and that filters do not filter selectively and after filtering out more than 25 per cent of the smoke particles produce an insipid smoke.

One way of modifying the pyrolytic process is by controlling the burning temperature, as suggested by Lam.[141] The temperature of the combustion zone of cigarettes has been measured in several studies. Wynder's initial report recorded temperatures up to 966° C. and averaging 682° C.[262] In more recent work by Touey and Mumpower,[248] who used platinum and platinum-rhodium thermocouple wires, the burning temperatures of cigarettes averaged 884° C., with a range from 854° to 913° C. Variations in tobacco blend, cigarette size, and puffing pattern had little effect on the temperature. Ermala and Holsti[68] had noted lower burning temperatures for cigarettes as smoked by a moderate smoker (average 650°, maximum 812° C.) and much lower for pipes (500° C. average) and cigars (range 380° to 630° C.). While the absolute values may be in error because of differences in thermocouple wires used, it is of interest that Greene[85] also found the combustion zone of pipes cooler (540° to 590° C.) than that of cigarettes (610° to 740° C.); cigars were intermediate (600° to 660° C.).

Wynder, Wright, and Lam[267] found that carcinogenesis from tobacco smoke condensate is greatest when pyrolysis has been carried out at more than 800° C. and that progressively fewer cancers are produced on animals by tar of tobacco pyrolyzed at lower temperatures. At lower burning temperatures, Croninger, Graham, and Wynder[43] found at least as much carcinogenic activity for mouse skin in cigar and pipe as in cigarette smoke condensates. Furthermore, Lindsey's group had found larger amounts of polycyclic hydrocarbons in cigar smoke[25] and pipe smoke[81] obtained in a manner simulating human smoking behavior.

Modification of pyrolysis can also be accomplished by chemical means. Alvord and Cardon[2] reported that the treatment of cigarette paper with ammonium sulfamate decreases the 3,4-benzpyrene of cigarette smoke. The group compared 3,4-benzpyrene produced by combustion of cigarette paper and tobacco and concluded that contribution of the paper was the more significant.[26,204] On a gram-for-gram basis, five times as much 3,4-benzpyrene was present in cigarette paper smoke as was found in tobacco smoke. Latarjet and others[145] also have reported a decrease in 3,4-benzpyrene content of tobacco smoke condensate after pretreatment of cigarette paper with ammonium sulfamate. Rand and associates[204] stated that tars from the paper produced cancer in mouse skin and that pretreatment of the paper with ammonium sulfamate reduced the

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amount of 3,4-benzpyrene by 98 per cent and prevented the disappearance of sebaceous glands in mouse skin which resulted from application of untreated tar. The claim that 4 per cent ammonium sulfamate when added to the cigarette paper significantly reduces the 3,4-benzpyrene in the smoke has not been substantiated, but large amounts of the substance added to the tobacco will do so.[246]

Cooper, Gilbert, and Lindsey[37] measured the concentration of several polycyclic hydrocarbons in smoke from "cigarettes" made from cigarette paper and found 4 μg of 3,4-benzpyrene per 100 Gm. of paper. While this is a higher concentration than found in tobacco, the paper was estimated to contribute only about 17 per cent of the 3,4-benzpyrene found in cigarette smoke.

The British Tobacco Manufacturers' Standing Committee reported that copper nitrate and platinum diaminonitrite reduce the benzpyrene content of cigarette smoke,[246] but full details of the work are not available.

Comment.—Neither Doll and Hill[56] nor Hammond and Horn[103] designed their study to examine the effect of withdrawal from smoking. While their results are highly suggestive, questions of the dose of smoke received by continuing and giving up smoking and differences in the duration and characteristics of smoking habits make it difficult to attach significance to the data on this point with confidence. Randomization of control and experimental groups would be required to assure validity of the implied interpretation that the effect of smoking is reversible. Efforts in preventive measures, other than those directed at teenagers, are based on the assumption that the effect is reversible.

In the experiments described by Wynder, a few interesting questions are answered, but more are raised. How do the products of tobacco pyrolyzed anaerobically under laboratory conditions compare with those of a burning cigarette? What is the effect on the lungs of the additional products of tobacco pyrolysis which are produced at lower burning temperatures? How can the high carcinogen content and high carcinogenicity of pipe and cigar smoke with their lower burning temperatures be reconciled with the reduced carcinogenicity of tobacco pyrolyzed at lower temperatures?

DISCUSSION

Is there a body of evidence or a school of thought which offers a reasonable alternative explanation to the evidence implicating smoking of cigarettes as the major environmental etiological factor in lung cancer?

The literature shows that those who have discounted the significance of the statistical association between smoking and lung cancer have given different reasons for doing so. Rigdon[207] and Rigdon and Kirchoff[208-211] have frequently expressed the view that the increase in lung cancer is more apparent than real and has resulted from improved diagnosis over a period of years. Berkson first questioned the association,[8] then found it "incredible that smoking should cause all these diseases." He advanced hypotheses based on constitutional types and differences in "rate of living"[9] to account for variation between smokers and nonsmokers in incidence of certain diseases. Hueper[116,117] has emphasized industrial wastes as playing a highly significant causal role in the recent rise in lung cancer, and Kotin and Falk[132] have felt that atmospheric pollutants, particularly automobile exhausts, should be implicated because of urban-rural differences in lung cancer mortality rates and experimental evidence. Eastcott[64] has presented evidence for a similar concept which he refers to as urbanization.

Fisher,[74] accepting the association between smoking and lung cancer, suggests that those who choose to smoke are the type who genetically are prone to acquire lung cancer. Little[155,156] has recently leaned toward this latter view, although Kotin[129] has stated that "all available evidence points to a dominant etiological role for exogenous agents present in our respiratory environment."

There seems to be little agreement among those who have at some time minimized the importance of smoking in the lung cancer picture. At least eight* statements[23,110,119,171,174,233-235] have been made independently by officials and agencies responsible for evaluation of public health problems in five countries strongly implicating the smoking of cigarettes as a major causative factor in human lung cancer. There is little doubt that factors of susceptibility and resistance are influential in determining whether any individual will acquire the disease, although the data indicating differences in susceptibility to the effects of smoking are meager[205,224] and further research in this direction is strongly indicated.

Available data are highly suggestive that the risk of lung cancer as well as total mortality decrease progressively for those who have given up smoking. Of course, the possibility should be faced that those who have smoked for 10 to 20 years, if persuaded to give up the habit, might find that they did not thereby avoid lung cancer or materially improve their life span. In order to establish the value of cessation of smoking, a study based on *random* selection of a group of persons persuaded to give up smoking would be required. Most observers believe that such a study would be impractical because of the lack of cooperation which might be expected unless adequate incentives were furnished those persons asked to stop smoking.

Some of the difficulties and complexities of identifying and removing health hazards from cigarettes in making a "safe" cigarette have been discussed. While many carcinogens have been found in cigarette smoke, none are positively known to be responsible for human lung cancers. Major interest has been directed toward the polycyclic hydrocarbons of the neutral fraction, two of which are known to be carcinogenic to the lung. In addition to these, several other carcinogens have been identified which may play an important role in the development of human lung cancer. There is also inadequate knowledge of the parts played by stable free radicals in all fractions, by arsenic, by the carcinogenicity of acidic and basic fractions, by the irritants, and by "cocarcinogenic" factors, acids, and other effects of the smoke still at the stage of hypothesis. For example, according to Freedlander and French,[76] a niacin-deficient diet increases the production of both spontaneous and urethane-induced adenomas in strain A mice. Since cigarette smoke contains a number of compounds related to niacin, there has been speculation that some may have an antiniacin effect and decrease the level of the vitamin in humans.

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*Since this manuscript was submitted for publication, five comparable statements have been made or adopted by: the American Public Health Association (Oct. 21, 1959); a Study Group on the Epidemiology of Cancer of the Lung, World Health Organization (November, 1959); the National Tuberculosis Association (Feb. 8, 1960); the Canadian Cancer Society (February, 1960); and the Board of Directors of the American Cancer Society (J.A.M.A., March 26, 1960).

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It is impossible to assure the public of a simple correlation between amount of condensable smoke inhaled and the risk of lung cancer. Edwards[66] believes the evidence shows that "the harm done per cigarette per day decreases with increasing amounts smoked." Wynder's results would suggest that decreasing the *frequency* of application of cigarette smoke condensate to the skin of mice is more important in reducing the number of resulting cancers than the *amount* applied with each painting. If the experience of Wynder, Kopf, and Ziegler[264] on mouse skin were interpreted in terms of the human lung, one might expect 20 per cent fewer lung cancers from a filter cigarette with 34 per cent less condensable smoke. There is evidence that the assumptions necessary to make such a prediction may not be valid. A survey made by the Federal Trade Commission[89] showed that 30 per cent of those who had changed from regular to filter brands were smoking increasing numbers of cigarettes. Whether there were other ways of compensating for any effect of the filter, such as taking more puffs per cigarette or inhaling more deeply, has not been determined. Reduction of the total tar content of mainstream smoke obtained from mechanically smoked cigarettes has frequently been accomplished by various devices, including filters. So far such devices have either given a sense of protection without sufficient evidence of benefit or have been unacceptable to smokers.

The possibility exists that a method may be found which will allow selective removal or will prevent the formation of aromatic carcinogens present in the smoke of cigarettes. While such a solution might turn out to be a happy one with respect to cancer, smoking has been implicated in a number of other diseases. Attention should be paid to the possibility that an etiological relationship may eventually be established between smoking and death from coronary artery disease[22,56,63,103] and morbidity from tuberculosis[66,160] and peptic ulcer.[59,227] The agents responsible for these other diseases, if present in tobacco smoke, may be in fractions of the smoke other than those containing the carcinogens. A recent report by Farr and Revere[71] opens up the question of the role played by leaf debris, filter filaments, charcoal, and wood fibers found under light and electron microscopy in smoke particles collected from both filter and nonfilter cigarettes purchased on the open market and burned under standardized conditions simulating human smoking.

The "needs" and desires of present-day cigarette smokers can theoretically be satisfied without exposing them to the hazards of tobacco smoke. The problem is not how to remove tar from smoke. With the exception of some gases such as carbon monoxide, ammonia, hydrogen cyanide, and carbon dioxide,[124,125] tar *is* the smoke; it can be removed essentially in toto from the inspired air drawn through a burning cigarette.

It should not be assumed that all the diseases reported to be associated with smoking are necessarily causally related to smoking, but the conclusion seems unavoidable that total mortality rates are higher among smokers than nonsmokers[56,63,102] and that lung cancer deaths can account for only a fraction of the excess. Would it not be realistic to anticipate the likelihood that convincing experimental evidence will uphold a cause-effect hypothesis for other diseases as it has for lung cancer? If so, it is difficult to imagine a technique being

developed for the removal of each responsible agent without completely modifying the nature of the inhaled aerosol. The possibility of producing nonpyrolyzed aerosols of selected known compounds may hold the key to the monumental task of satisfying the semiaddicted smoker, a powerful industry, and the health of a large segment of the population.

CONCLUSIONS

The scientist is traditionally reticent about interpreting facts, but most physicians, public health officers, and the public are finding it quite reasonable to accept the belief that smoking is the major environmental causative factor in human epidermoid lung cancer. The evidence in favor of such a relationship is extraordinarily abundant and consistent. The several alternative suggestions are largely speculative and consistency among their proponents is lacking.

Because of the lack of adequate data to make an estimate of the true contribution of cigarette smoking to lung cancer, speculation based on the semiquantitative studies of several different types which have been discussed would place the number of cases associated with cigarette smoking in the range of three-fourths of all cases of primary lung cancer in this country. Estimates which would support this value as a conservative approximation have been presented. If this estimate is essentially correct, one could assume that, except for smoking, the lung cancer rate would not be higher than that of cancer of the bladder, responsible for approximately 7,200 deaths per year in the United States, instead of the 36,000 lung cancer deaths expected this year.

Air pollutants and host factors may be directly responsible for some lung cancers and may be essential features operating as adjuncts with smoking in others. A thorough, objective review of this subject is needed. Efforts should also be directed toward research on the etiology of the adenocarcinoma and bronchiolar carcinoma, which appear to be less of environmental than of endogenous origin.

The practical means of achieving any of the three methods which might be used in avoiding the health hazards of smoking—cessation of the habit among smokers, production of a safe cigarette, and production of an acceptable substitute for the pleasures derived from smoking—are not clear at the present time. For the majority of smokers, giving up smoking may be the most difficult way of avoiding the health hazards in cigarettes.

Modification of cigarettes sufficient to reduce materially the lung cancer hazard now present in smoking may eventually be achieved. That lung cancer may be only a relatively small, though important, portion of the total health hazard from smoking is evidenced by the correlation between history of smoking and total death rates consistently found in three prospective studies.

It now seems most practical to think in terms of prevention of diseases known and suspected to be etiologically related to smoking, rather than in terms of prevention of a single disease. It also seems most *realistic*, insofar as possible, to try to preserve the pleasures and habit patterns into which such a large segment of the civilized world has become enmeshed, without sacrificing their health.

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Both these objectives can be achieved through elimination of exposure to the known and suspected hazards of smoking while substitutes acceptable to the smoking population are provided.

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APPENDIX A

The fact that three prospective studies have corroborated the findings of so many retrospective studies that demonstrate a correlation between cigarette smoking and lung cancer raises the question of whether the limitations of retrospective studies are as great as suggested by Berkson,[9] Dorn,[61] Hammond,[96] and Hammond and Horn.[100] Berkson's paper on the limitations of the application of fourfold table analysis to hospital data[7] was referring to so-called retrospective studies. In his 1955 paper, he demonstrated that a prospective study does not necessarily avoid the pitfalls of selection which can occur in such a retrospective study.

Dorn enumerated three criticisms of retrospective studies on the grounds of (1) the fact that persons are not interviewed on the basis of probability sampling, (2) the lack of direct measure of the risk of developing lung cancer, and (3) the possibility of psychologic bias in some instances in an interviewer who knows the diagnosis. It is of interest that none of the prospective studies were on probability samples of a population. In the light of the publicity on the subject of smoking and lung cancer which preceded most of the retrospective studies, it would be expected that the psychologic bias of a patient with lung cancer would be to minimize his smoking habits rather than to exaggerate them. This bias would operate against the hypothesis of a cause-effect relationship between smoking and lung cancer in retrospective studies.

Hammond recognized the follow-up procedure as time consuming and extremely expensive. As arguments against retrospective studies he listed (1) psychologic biases in subject and interviewer, (2) biases of selection of comparable experimental and control groups, and (3) the statistical fallacy pointed out by Berkson.[8] Mainland and Herrera[167] have expressed the opinion that psychologic bias is a risk present when either professional or nonprofessional interviewers are asked to select the subjects for study.

From the above discussion it appears that the limitations of retrospective studies have not always been implicit in the method.[149] Retrospective and prospective studies serve different purposes. In this case retrospective studies have examined the characteristics of a disease, lung cancer. The prospective studies have been on smoking. They have been particularly valuable in demonstrating the increased over-all mortality rates found among smokers as well as those of several specific diseases.

APPENDIX B

Studies of Biologic Effects of Tobacco Smoke and Its Condensates

ANIMAL	SITE	TEST	AUTHOR REFERENCE NUMBERS
Mice	Skin	Painting	37, 78, 87, 94, 174, 189, 196, 240, 242, 262, 263
		Sebaceous gland	4, 43
		Inhalation	5, 69, 139, 146
	Lung	Pellets	139
		Thread fixation	139
	Cervix	Painting	122
	Bladder	Oral administration	113
Rats		Injection (intratracheal)	139
		Inhalation	139, 172
	Lung	Injection (transpleural)	13
		Pellets	139
		Thread fixation	139
Rabbit	Lung	Inhalation	112
	Skin	Painting	84, 266
Dog	Lung	Painting of bronchus	213
Hamster	Lung	Instillation	49
	Oral pouch	Painting	178
Fowl	Lung	Smoke inhalation	197
Newt	Tail	Subcutaneous injection	182
Human	Fetal lung	Tissue culture	143
	Adult lung	Inhalation	3, 29

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MORTALITY FROM CORONARY HEART DISEASE IN CALIFORNIA MEN WHO WORK LONG HOURS

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THIS report presents the mortality from arteriosclerotic-coronary heart disease in California men, ages 25 to 64, in relation to one form of occupational stress. The purpose is to see whether the results support the finding by Russek and Zohman[1] that an unusually large proportion of coronary heart disease patients had excessively long work hours for some time preceding the attack.

Analysis of California occupational mortality data for 1949 to 1951 showed, as reported elsewhere,[2] a moderate increase in mortality from coronary heart disease associated with a limitation of physical activity in work as determined by classifying occupational reports on death certificates. The same occupational data are used here in a different arrangement for the test of job stress.

Our earlier report contains a general description of the sources and limitations of the data and only a few points require repetition at the outset. For the three years 1949 to 1951, there were 72,664 deaths of California men aged 20 to 64, of which 22,176 deaths were attributed to arteriosclerotic, including coronary, heart disease (I.S.C. 420) occurring at ages 25 to 64. A ratio was established between the number of deaths in each occupation (as recorded on the death certificate) and the Census enumerations of men in each occupation in California, 1950. The magnitude of risk was then measured by the standardized mortality ratio (S.M.R.), that is, the ratio of the observed deaths in an occupation to the number of deaths expected if the persons in each occupation would have experienced, in each age group, the mortality of the persons in all occupations.

Normally the S.M.R. for all men is 100. Since we have not adjusted for the unreported occupations on death certificates, the S.M.R. for all reported occupations will range slightly under 100, as shown in the tables. All S.M.R.s are based

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on at least 50 observed deaths unless otherwise indicated in the tables. Age-specific rates used for computing the standardized mortality ratios are shown in the earlier report. Age group 25 to 44, combined here, is internally adjusted.

There is an apparent discrepancy in the data in that the California death certificate during 1949 to 1951 requested the occupation held longest by the decedent, while the 1950 Census of population enumerated the *last* occupation of men. It was found,[2,3] however, that *last* occupation was more frequently entered on the death certificate, so that a computation of death ratios seems justified. Where last occupation was not reported, the amount and direction of error do not influence the results sufficiently to alter their interpretation. This is shown in detail in the Appendix.

HYPOTHESIS

Russek and Zohman[1] reported on a retrospective study which showed an apparently greater frequency of job stress in 100 young coronary heart disease patients, aged 25 to 40, than in 100 controls of similar age, occupation, and ethnic origin. The investigators stated that 91 per cent of the coronary patients had been under occupational stress of some kind prior to onset of the clinical symptoms. Of these, 25 per cent held a second job in addition to a regular, full-time job; an additional 46 per cent had worked 60 hours or more a week for long periods preceding attack; another 20 per cent had unusual fear, insecurity, discontent, etc., in relation to employment. In contrast, the authors report a total of only 20 per cent in the control series having comparable occupational stress, without stating the proportions having each characteristic.

The California death certificate data can be used to test part of this reported finding, namely, the apparently increased risk of the disease associated with work beyond 48 hours a week. This is possible because a 1950 Bureau of the Census publication[4] provides information on the numbers of men in each occupation in the United States who reported working stated numbers of hours during the week of the 1950 Census. (There is, of course, a seasonal effect on work hours, because the Census takes place in the spring, and a possible regional difference, since the Census information is for the United States as a whole.)

There appears to be a substantially increased risk of coronary heart disease associated with the work experience of long hours, according to the Russek data. One can make a rough estimate of the amount of apparently increased risk in the following way. Assume, in the absence of more detailed information, that all 20 per cent of the controls with occupational stress worked over 48 hours a week (the 1950 Census data indicate that 25 per cent of men of all ages work more than 48 hours a week). The proportion of coronary patients working over 48 hours a week would range from 46 per cent (those working at least 60 hours) to 46 per cent plus 25 per cent (men with a second job in addition to a full-time job, some portion of whom will accumulate over 48 hours of work per week). The actual case-control difference would then fall between 46 and 20 per cent and 71 and 20 per cent. If the assumptions involved in using Cornfield's[5] formula for estimating relative risk from case-control data could be met by the Russek

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study, these differences would correspond with relative risk ratios of 3.4 to 1 and 9.8 to 1. That is, there would appear to be from three times to ten times more risk of the disease among those working more than 48 hours a week than among those not working over 48 hours a week.

It is not possible to evaluate all potential biases that may have influenced these estimates from case-control data, but one possible source of bias can be noted. The work experience of the patients was determined after coronary heart disease was apparent, with most of the interviews taking place during late convalescence. The obvious difficulty of the method is that coronary patients, because of their illness, may emphasize or exaggerate the extent to which they had overworked themselves. In addition, the method had the effect of eliminating from consideration those who died at or shortly after their first attack. Morris and co-workers'[6] incidence surveys of postal and civil service workers suggest that from 30 to 50 per cent of first attacks of coronary thrombosis cause death within the first 3 months, most of this within a month. This suggests that Russek and Zohman's cases may be unrepresentative of total incidence. However, the finding of such a substantial excess risk as estimated above merits further investigation. If the experience of working more than 48 hours a week actually contributes to total incidence of coronary disease, a study of registered mortality should also detect an association. Such data would comprise both the rapidly fatal cases and the deaths from coronary heart disease after survival of earlier attacks, but would exclude cases in which death ultimately occurred due to other causes.

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We have analyzed the California registered mortality in the following way. According to the Census enumeration mentioned above, about 25 per cent of all men reported working more than 48 hours a week. Proportions for the specific occupations range from about 3 per cent to 66 per cent. The occupations have been placed in sequence of increasing proportions and then separated into five classes: 0 to 9, 10 to 19, 20 to 29, 30 to 39, and 40 and over per cent of persons in each occupation working more than 48 hours a week. This sequence represents not a variable of increasing stress, but of increasing proportions of men at special risk from stress, if the hypothesis is correct.

It should be noted that the occupations are identified according to the proportions of men supposedly at risk, while decedents are identified only according to occupation. The method is not an exact one. If, for example, the class of occupations with an average of 35 per cent of men "exposed" had a mortality rate higher than the class with 25 per cent of men "exposed," we could not be sure that the excess 10 per cent of the men were those who contributed to the increased risk. While the method has its limitations, it may be useful in evaluating an already reported finding. We can say that, if the hypothesis is correct, the rates should increase with increasing proportions of men at risk.

RESULTS

Stress.—The relationship of job stress, that is, working more than 48 hours a week, to the mortality risk from arteriosclerotic-coronary heart disease is

TABLE I. STANDARDIZED MORTALITY RATIOS FOR OCCUPATIONS RANKED BY PERCENTAGE OF MEN WORKING MORE THAN 48 HOURS A WEEK, CALIFORNIA, 1949 TO 1951

AGE AND CAUSE OF DEATH	ALL REPORTED OCCUPATIONS*	ALL NONFARM OCCUPATIONS	PERCENTAGE WORKING MORE THAN 48 HOURS A WEEK						
			0-9%	10-19%	20-29%	30-39%	40+%		
							NON-FARM	FARMERS	FARM LABORERS
20-64									
Arteriosclerotic and coronary heart disease	97	101	97	89	103	117	108	83	51
All other causes	95	96	107	83	95	95	80	98	107
25-44									
Arteriosclerotic and coronary heart disease	98	101	95	93	105	110	115	89	(47)†
All other causes	95	93	103	86	102	82	67	112	142
45-54									
Arteriosclerotic and coronary heart disease	98	101	98	89	106	113	105	87	53
All other causes	95	96	110	83	93	95	76	100	107
55-64									
Arteriosclerotic and coronary heart disease	97	101	97	88	101	121	109	82	51
All other causes	95	97	107	82	91	103	91	94	85

*S.M.R. for all occupations including unreported is 100.
†Number in parentheses is based on less than 50, but more than 25, observed deaths.

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shown for each age group in Table I. The table also shows the relationship with mortality from all other causes combined.

Table I shows S.M.R.s for occupations which are grouped according to proportions of men working over 48 hours. The class of occupations with 40 and over per cent working long hours has been separated into nonfarm and farm occupations, the latter including both farmers and farm laborers. These farm occupations, shown in Table I, disclose some protection from mortality due to arteriosclerotic-coronary heart disease. The main discussion of results to follow excludes the farm occupations partly because of evidence[3] that farmers are considerably overreported and farm laborers underreported on death certificates in California; partly because they are distinguished by an additional environmental factor, rural living. Nevertheless, it is important to note that long hours of farm labor do not lead to elevated mortality rates from arteriosclerotic-coronary disease.

Nonfarm occupations do, however, show some evidence of higher rates with longer work hours. Considering all nonfarm occupations in Table I, age group 25 to 44 years reveals a fairly regular increase in arteriosclerotic-coronary mortality rates corresponding to an increase in the proportion of men working long hours. Russek and Zohman cite their evidence from data involving approximately the same age group, ages 25 to 40. At ages 45 to 54 and 55 to 64, however, the rate increases in the same direction are irregular, being especially inconsistent at either end of the gradient for arteriosclerotic-coronary disease.

Mortality from all other causes combined appears to vary independently of arteriosclerotic-coronary heart disease at ages 25 to 44. In the oldest age group, 55 to 64, the pattern of variation is somewhat similar to that for arteriosclerotic-coronary heart disease.

Stress and Physical Activity.—It seems worth inquiring whether long work hours are more likely to constitute a hazard of increased risk in certain kinds of occupations. In Table II the results are shown within each physical activity level of job. The classification of occupations by four levels of physical activity, discussed in a previous article,[2] corresponds only crudely to the actual work experiences of men in these occupations.

Light Workers.—Table II shows that occupations of light physical activity have mortality rates from arteriosclerotic-coronary heart disease that increase somewhat regularly with greater proportions of men working long hours. Again the increase is quite consistent at ages 25 to 44. At ages 45 to 54 and 55 to 64 the gradients, while still irregular, show less inconsistency than appeared for all physical activity classes combined. The class with only 0 to 9 per cent working long hours has an appropriately lower rate. The rate of mortality from all other causes does not increase in the same way for light workers except in the oldest age group, 55 to 64, where the rate shows a tendency to parallel that for arteriosclerotic-coronary mortality.

Sedentary Workers.—The trends for these workers are unlike the trends for light workers, except for a similar increase on the stress gradient for arteriosclerotic-coronary mortality rates at ages 25 to 44, based on quite small numbers.

It should be noted that none of the sedentary occupations has as many as 30 per cent of men reporting work in excess of 48 hours a week.

Medium and Heavy Workers.—The variations in rates for all medium workers were quite similar to those for all heavy workers, so we have combined the two groups in Table II. This combined group fails to show a consistent increase in

TABLE II. STANDARDIZED MORTALITY RATIOS FOR OCCUPATIONS RANKED BY PERCENTAGE OF MEN WORKING MORE THAN 48 HOURS A WEEK AND BY PHYSICAL ACTIVITY, CALIFORNIA, 1949 TO 1951

CAUSE OF DEATH, AGE, AND PHYSICAL ACTIVITY	ALL NONFARM OCCUPATIONS	PERCENTAGE WORKING MORE THAN 48 HOURS A WEEK				
		0–9%	10–19%	20–29%	30–39%	40+% (NONFARM)
Arteriosclerotic and Coronary Heart Disease						
25-44						
Sedentary	86	83	(87)*	(94)		
Light	101	78	93	108	110	115
Medium and heavy	105	108	94	107	111	†‡
45-54						
Sedentary	105	108	(116)	96		
Light	103	83	100	114	113	103
Medium and heavy	97	101	76	103	112	(172)‡
55-64						
Sedentary	98	101	86	96		
Light	106	78	105	110	120	107
Medium and heavy	96	104	73	86	125	206‡
All causes except Arteriosclerotic and Coronary Heart Disease						
25-44						
Sedentary	65	68	66	53		
Light	73	68	77	99	67	67
Medium and heavy	123	134	97	124	121	(72)‡
45-54						
Sedentary	75	84	75	57		
Light	97	77	80	103	83	76
Medium and heavy	118	132	86	107	135	(88)‡
55-64						
Sedentary	81	84	80	77		
Light	88	75	87	95	94	90
Medium and heavy	112	127	78	97	138	131‡

*Numbers in parentheses are based on less than 50, but more than 25, observed deaths.
†Fewer than 25 observed deaths.
‡Only one occupation, firemen in fire protection, which is classified as medium physical activity.

arteriosclerotic-coronary mortality rates with increasing proportions of men working long hours. This is true in each of the three age groups. There would appear to be, however, consistent trends if there were not the unusual fluctuations produced by high S.M.R.s, for both cause-of-death groups, in the class with the fewest (0 to 9 per cent) working long hours. The rate then drops markedly in the next group (10 to 19 per cent) and increases regularly after that. The mortality

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from all other causes follows closely the variations in mortality from arteriosclerotic-coronary heart disease in these medium and heavy workers.

Physical Activity and General Mortality Liability.—Though we stated in the introduction that an earlier study[2] revealed a moderate association between a limitation on physical activity and higher mortality from arteriosclerotic-coronary disease after age 45, Table II fails to show that association. This is because an association of moderate degree is readily apparent in the California data only in comparisons of occupations having a similar general mortality liability. The existence of some risk factor, or factors, common to mortality from several diseases appears to have an obscuring effect on the association. This obscuring effect was found to be powerful because general mortality was associated with greater physical activity and arteriosclerotic-coronary mortality with lesser physical activity.

In the present problem, general mortality is not associated with stress in a direction opposite to the expected association of stress with arteriosclerotic-coronary disease. Consequently there cannot be the same strong obscuring effect. In fact, Table II shows some tendency for mortality from all other causes to vary along with mortality from arteriosclerotic-coronary disease for medium and heavy workers at older ages. Therefore, a control on general mortality risk does not consistently strengthen the evidence of an association between stress and arteriosclerotic-coronary mortality.

Heart Disease Specifying Coronary Arteries (420.1).—This classification of cause of death is used when the death certificate mentions myocardial infarction and coronary thrombosis, among other conditions. It represents 84 per cent of the total heart disease deaths considered here, with the remainder classified as "arteriosclerotic heart disease, so described" (420.0). In the earlier analysis of the relation with physical activity of work, a limitation of activity was more strongly associated with heart disease specifying coronary arteries than with arteriosclerotic heart disease, so described.

The previous tables have been for total arteriosclerotic, including coronary, heart disease deaths (420). The analysis separately for coronary heart disease is shown in Table III, which reveals gradients differing very little, if any, from gradients shown for total arteriosclerotic-coronary disease. At ages under 45, however, very few deaths are attributed to arteriosclerotic heart disease, so described, as shown in the earlier report.[2] Therefore the most pronounced gradient, that for light workers at ages 25 to 44, is primarily an association with coronary heart disease including reported myocardial infarction and coronary thrombosis.

Magnitude of Increased Risk.—If there is a consistent gradient among light workers at ages 25 to 44, the S.M.R.s in the stress classes should vary in a manner determined by the amount of increased risk associated with stress and by the proportions of men in each class who are subject to the presumed increased risk. We know the proportions of men at increased risk; we can estimate the magnitude of increased risk that would produce the progressively higher S.M.R.s in each stress class. This is shown below.

Of all light workers, 26.5 per cent reported working more than 48 hours a week. (The Census publication[4] does not give age-specific information on work

hours and we are assuming that 26.5 per cent, true for light workers of all ages, is approximately correct at ages 25 to 44.) If the hypothesis we are testing is true, the average S.M.R. for all light workers at ages 25 to 44 should be approximated by the S.M.R. in the class "20 to 29 per cent" (midpoint 25) working more than 48 hours because this class would be most like the total group in the proportion at a presumed excess risk. Table III shows the average S.M.R. for all light workers ages 25 to 44 to be 101 (column 1), and the S.M.R. for the class "20 to 29 per cent" is in close agreement, 100 (column 4).

The degree of relative risk associated with stress, and which would produce the gradient in question for light workers, can be estimated in the following way. In the classes with 0 to 9, 10 to 19, etc., per cent working long hours, averages (midpoints) of 5, 15, etc., per cent are at an increased relative risk if 95, 85, etc., per cent are assumed to be at unit risk. That is, the amount of risk due to all other factors is taken as unity. Theoretic S.M.R.s can then be determined for increased risks of various magnitudes for stress, setting, as explained above,

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TABLE III. STANDARDIZED MORTALITY RATIOS FOR CORONARY HEART DISEASE; OCCUPATIONS RANKED BY PERCENTAGE OF MEN WORKING MORE THAN 48 HOURS A WEEK AND BY PHYSICAL ACTIVITY LEVEL, CALIFORNIA, 1949 AND 1951

AGE AND PHYSICAL ACTIVITY	ALL NONFARM OCCUPATIONS	PERCENTAGE WORKING MORE THAN 48 HOURS A WEEK				
		0–9%	10–19%	20–29%	30–39%	40+% (NONFARM)
25-44						
Sedentary	85	83	*	102		
Light	101	85	94	100	105	121
Medium and heavy	106	110	95	109	102	†
45-54						
Sedentary	108	110	(126)‡	99		
Light	103	78	99	117	117	102
Medium and heavy	96	102	74	101	108	(187)†
55-64						
Sedentary	104	106	84	106		
Light	106	79	101	107	124	108
Medium and heavy	94	101	69	92	123	(212)†

*Based on fewer than 25 observed deaths.
†Only one occupation, firemen in fire protection, which is classified as medium physical activity.
‡Numbers in parentheses are based on less than 50, but more than 25, observed deaths.

an average S.M.R. of 100 in the class "20 to 29 per cent." For example, given a twofold increased risk for 25 per cent of a class: $25(2) + 0.75(1) = 1.25$; and for 5 per cent of a class: $0.05(2) + 0.95(1) = 1.05$. Then $1.05/1.25(100) = 84$ as the S.M.R. in the class with an average of 5 per cent (0 to 9 per cent) of men at increased risk. This is done in Table IV which compares the actual S.M.R.s with theoretic S.M.R.s calculated for relative risk ratios of 1.5, 2.0, and 2.5.

Actual S.M.R.s agree fairly well with theoretic results for a twofold increased risk. This indicates that among workers in light physical activity, ages 25 to 44, those who work more than 48 hours a week have twice the risk of mortality from coronary heart disease compared to other light workers.

We have not attempted estimates of the size of increased risk for light workers at older ages because the results, while suggesting an association, do not demonstrate an orderly progression of rates. There may be one or more kinds of influences which interfere with the observation of a risk association, if in fact it exists, at these older ages.

TABLE IV. ACTUAL AND THEORETIC S.M.R.S FOR CORONARY HEART DISEASE IN LIGHT WORKERS, AGES 25 TO 44

CLASSIFICATION	ALL LIGHT WORKERS	PERCENTAGE WORKING MORE THAN 48 HOURS					
		0–9%	10–19%	20–29%	30–39%	40–49%	50–59%
Actual S.M.R.	101	85	94	100	105	121*	
Theoretic S.M.R.s:							
If risk is 1.5 fold		91	96	100	104	109	113
If risk is 2 fold		84	92	100	108	116	124
If risk is 2.5 fold		78	89	100	111	122	133

*Actual S.M.R. for the open-end class "40+ %" which has a midpoint greater than 45.

DISCUSSION

The mortality risk from coronary heart disease appears to be greater among men who work more than 48 hours a week in certain occupations. The evidence from the California registered mortality, and from the case-control data of Russek and Zohman, is summarized here.

1. The strongest evidence of an association in the California data is found among men at ages 25 to 44, with less firm evidence after age 45. Russek and Zohman, who published no data on older men, reported the association for ages 25 to 40.

2. In the Russek-Zohman study, the number of hours on the job was determined after coronary heart disease was diagnosed. The California study provided an independent means of checking that method: the coronary mortality was routinely registered and could have no influence on the separately determined Census information for number of work hours.

3. The Russek-Zohman study was made only on survivors of first attack. The California mortality included the victims of first attack, plus survivors who died of the disease later.

While we found the evidence to be more definitive when considering light workers alone, we cannot say that stress is a factor *only* at this level of physical activity of work. In part the result may be a function of the method. If one

could start in a different way, say by classifying men according to their weekly work-time experience, and then subclassify by occupation, many of the occupations in medium and heavy activity might be implicated insofar as the men in them work long hours. One reason to suspect this is the presence of high coronary mortality rates in medium and heavy occupations having over 30 per cent working more than 48 hours a week.

Considerably weaker evidence after age 45 certainly raises questions. Some may assert that coronary heart disease at ages under 45, where the stress hypothesis appears to be supported, is so unusual that it should not be the subject of a main hypothesis; evidence based on a population where the disease strikes with the greatest force would be preferable. But another point is at least equally impressive to us: if multiple causes are involved, a single risk-associated factor may be easier to detect where the disease is less frequent. Also, age itself may be a variable in determining what environmental factor among several will play a stronger part in elevating the risk of a disease.

One should note further questions about the differences in evidence before and after age 45. First, the length of the work week probably changes with advancing age and this would undoubtedly influence the observations. Second, the disease may be fatal before age 45 to the susceptible men who work long hours, leaving a group that is more resistant to mortality from the disease. As we see it, neither of these possibilities would invalidate the results.

A third possibility comes from the work of Rosenman and Friedman. In pointing out that atherosclerosis and infarction due to thrombotic complications "are, in part, separate entities," they suggest that the "occurrence of thrombosis, particularly in younger persons, may be only partly related to the severity of the underlying atherosclerotic changes."[7] Since atherosclerosis may not be well advanced under age 45, the experience of long work hours may bear no relationship to atherosclerosis itself but may increase the risk of thrombosis. The weakening of the association at older ages may be due to the existence of several sources of increased risk in the later years of life associated with several pathologic conditions which are only partially interrelated.

The relationship between stress and limitation of physical activity in work may be a complex one. Based on the data of this report and the earlier report on physical activity, all one can say is that stress shows a pronounced association with coronary disease in light workers before age 45, and a restriction of physical activity shows a moderate association after that age. Furthermore, the association with physical activity is detected only when the general mortality risk level of an occupation is controlled, whereas stress, as defined, is not clearly associated with the general mortality risk of occupations. These two factors might have, we think, different relationships with coronary heart disease: physical activity may provide some protective effect against the disease, while the stress of long work hours may have an active effect in bringing about the pathologic state.

Whether the experience of long work hours is itself a real cause is another question. Some skepticism is justified since there is almost certainly a selective recruitment into occupations. Occupations which call for an excess of work hours may be actively sought by men with the appropriate dispositions for the work.

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This is at least in harmony with the notion that the individual with a sustained or compulsive drive to reach his goals is a candidate for the disease—the interpretation offered by Russek and Zohman. This does not eliminate the possibility that the important factor is some basic change in the technical and emotional conditions of work. Men with a sustained exposure to long hours of nonfarm work might show a high rate, irrespective of their constitutional make-up.

The association between a long work week and an increased mortality from coronary disease does not lend itself to an unequivocal interpretation. At the same time a concept of occupational stress as a possible precursor of the disease is hardly a well-developed one. The use of objective indicators such as that employed here to check on Russek and Zohman's results and the idea of a "deadline" work pace used by Rosenman and Friedman[7] may be useful means of opening up the problem.

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SUMMARY

The registered mortality of men in California, 1949 to 1951, is used to test the hypothesis that occupational stress, insofar as it can be measured by the length of the work week, is associated with coronary heart disease. That measure has been used by Russek and Zohman,[1] who reported that a high proportion of persons with coronary heart disease had worked long hours for some time preceding attack. The registered mortality data, together with some Census occupational data on work hours, allows an independent check of that finding.

Farmers and farm laborers show relative protection from mortality attributed to coronary heart disease, even though many of them work long hours. On the other hand, evidence from nonfarm occupations shows an excess of coronary mortality among light workers who are on the job more than 48 hours a week, especially before age 45. The evidence for men at ages 45 to 64 is weaker and perhaps questionable; but, it should be noted, Russek and Zohman also report evidence only for young adults. The difference in the evidence for younger and older middle-aged men is open to several interpretations: perhaps the most useful to research is that stress, as defined, may be associated with thrombotic complications but not necessarily with progressive atherosclerosis of the coronary arteries.

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APPENDIX

The possible bias in the statements of occupation on death certificates in 1950 has been studied with limited data and reported by Buechley and colleagues.[3] Occupational histories taken by interview with several hundred lung cancer patients were compared with the occupations later entered routinely on the death certificates of the patients. This provided rough estimates of bias in the reporting of *last* occupation on the death certificate; the same data is available to us.

With occupations collected into the stress classes used in the analysis of mortality, we have established the ratio of the number of occupations actually reported on the death certificates to to the number of *last* occupations that should have been reported according to the histories. These ratios for each of the classes, 0 to 9, 10 to 19, 20 to 29, 30 to 39, and 40 and over per cent working long hours, were, respectively: 113/111 = 1.02, 74/75 = 0.99, 34/41 = 0.83, 51/55 = 0.93, 9/8 = 1.12. These ratios do not suggest a serious influence of occupation-reporting bias. As we have stated elsewhere,[2] underenumeration in an occupation at Census time may have some unknown effect on the S.M.R.s.

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Therapeutics

THALIDOMIDE—A NEW NONBARBITURATE SLEEP-INDUCING DRUG

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THALIDOMIDE* is the generic name for N-phthalyl-glutamic acid imide, a compound which has been employed in Europe for several years as a sedative-hypnotic. It is chemically related to glutethimide (Doriden), another sedative-hypnotic, and to bemegride (Megimide), a convulsant analeptic.

Unpublished data supplied by the Scientific Division of The William S. Merrell Company indicate that thalidomide is a central nervous system depressant in mice, reducing spontaneous motor activity slightly in doses of 30 mg. per kilogram and to a considerable degree in doses of 100 mg. per kilogram. Thalidomide at doses of 100 mg. per kilogram, orally or intraperitoneally, does not produce loss of righting reflexes in mice, rats, cats, dogs, or monkeys. Large quantities of drug (up to 4 Gm. per kilogram), by mouth or intraperitoneally, failed to produce death in mice over a 72-hour observation period. This lack of toxicity of large doses is most likely related to the insolubility of the compound and a consequent limitation in absorption.

Uncontrolled German trials[1-4] have reported thalidomide to be an effective hypnotic drug when administered in doses of 50 to 200 mg. In a controlled English trial by Salter, Lodge-Patch, and Hare,[5] 50 or 100 mg. of drug has been reported to produce sleep as quickly as 200 mg. of secobarbital, and the duration of sleep after 100 mg. of the thalidomide was found to be significantly greater than that after 200 mg. of secobarbital. The latter drug in turn produced significantly longer sleep on the average than did 50 mg. of thalidomide. No placebo treatment was included in the English trial. The authors reported that "moderately severe" hangover could occur after thalidomide, especially with the 100-mg. dosage.

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*Kevadon is a trademark of The William S. Merrell Company, Cincinnati, Ohio, for its brand of thalidomide, supplies of which were generously made available to us by Dr. R. C. Pogge.

METHODS

The present study compares two doses of thalidomide with placebo in a group of medical and surgical ward patients at the Johns Hopkins Hospital. Medical patients were chosen for study if they were considered by the nursing and house staff to present a sleep problem. Surgical patients were studied on their first night in the hospital; patients admitted for elective surgery, free of pain, and not requiring other medication were used exclusively.

Patients were interviewed during the day to elicit information about their underlying disease, the nature of their sleep problems and past exposure to hypnotic drugs, the presence or absence of pain, and their usual subjective state on awakening in the morning. (This last bit of data was utilized as a base line against which to assess any postdrug complaints by a patient on the morning after the actual experiment. Certain patients complain of headache, tiredness, sleepiness, dizziness,

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TABLE I. MEAN SLEEP INDUCTION TIME (MINUTES)

PATIENT GROUP	PLACEBO (POOLED)	THALIDOMIDE	
		100 MG.	200 MG.
Those whose usual induction time was less than 30 minutes	26 (N = 17)	32 (N = 15)	11 (N = 10)
Those whose usual induction time was 30 minutes or more	81 (N = 24)	100 (N = 10)	30 (N = 15)
All patients	58 ± 10.3 (N = 41)	59 ± 16.8 (N = 25)	23* ± 4.9 (N = 25)

*Significantly different from placebo and 100 mg. of thalidomide at 0.05 level.

etc., on awakening, whether or not a drug has been given, so that the true incidence of drug-related hangover may be overestimated if this precaution is not taken. The data on side effects to be reported therefore include only complaints clearly distinguishable from the normal subjective state without drug.)

Patients suitable for study were given, at bedtime, in randomized fashion, either placebo (single capsule), placebo (two capsules), 100 mg. of thalidomide (one capsule), or 200 mg. of thalidomide (two capsules). The next morning, patients were interviewed again and asked how long they estimated it had taken them to fall asleep, how long they had slept, and how they felt on awakening. Any spontaneous reports regarding the occurrence of untoward effects at other times were also recorded. If a patient failed to sleep at all or had to be given another sleeping medication during the night to induce sleep, the induction time of such a patient was arbitrarily called 240 minutes and the duration of sleep zero hours, to allow computation of means. The high correlation between "subjective" patient reports and "objective" reports by nurses or technicians has been described in previous papers.[6-8]

RESULTS

Previous studies in this laboratory have revealed a relationship between sleep performance under drugs (or placebo) and "usual" sleep habits without drugs; patients who ordinarily sleep poorly are more likely to sleep poorly under drugs than patients who ordinarily sleep well. The data are therefore presented in Tables I and II both as total mean scores and as subgroup scores. The patients are stratified for the sleep induction analysis into those who claimed to fall asleep usually in less than 30 minutes and those who claimed to require 30 minutes or more. For the duration of sleep analysis, the stratification is on the basis of usual sleep duration without drugs of less than 7 hours versus usual duration of 7 hours or more. These dividing points were chosen in both cases because they were convenient for dividing the groups into two roughly equal parts. Because the means for the two placebo groups did not differ significantly either in regard to induction or duration of sleep, the placebo data were pooled.

TABLE II. MEAN TOTAL DURATION OF SLEEP (HOURS)

PATIENT GROUP	PLACEBO (POOLED)	THALIDOMIDE	
		100 MG.	200 MG.
Those whose usual duration of sleep was 7 hours or more	6.7 (N = 24)	7.2 (N = 13)	7.6 (N = 14)
Those whose usual duration of sleep was less than 7 hours	5.1 (N = 17)	4.5 (N = 12)	7.1 (N = 11)
All patients	6.1 ± 0 .35 (N = 41)	6.2 ± 0.50 (N = 25)	7.4* ± 0.20 (N = 25)

*Significantly different from placebo and 100 mg. of thalidomide at 0.05 level.

Tables I and II show that the smaller dose of thalidomide was not significantly different from placebo either in inducing sleep or in prolonging it, whereas 200 mg. of drug produced effects significantly better ($P < 0.05$) than either placebo or 100 mg. of drug for both parameters. Each treatment shows the differential effect alluded to before, i.e., better performance in the "low-challenge" groups than in the "high-challenge" groups, but the higher dose of thalidomide differs from the other two treatments in its impressive over-all performance.

Side effects were more common in the drug groups. Only one of the 41 patients given placebo described a side effect of any sort, a feeling of drowsiness on awakening in the morning. Of the 25 patients on the 100-mg. dose of thalidomide, 1 patient complained of having to urinate six to seven times during the night, another felt dizzy in the morning, another felt drowsy on awakening and went back to sleep for 1 hour, and the fourth patient complained of headache, drowiness, and "tiredness" on the morning after taking drug. Of the 25 patients

who received 200 mg. of thalidomide, 2 felt slightly drowsy on awakening, 1 felt dizzy and confused during the night and had headache and residual drowsiness in the morning, and the fourth woke up after 2 hours of sleep with severe nausea, went back to sleep after 1 hour, and had residual nausea in the morning.

DISCUSSION

Our data indicate thalidomide to be a potent hypnotic, and the mean figures for the 200-mg. dose are similar to what we have come to expect from an equal dose of secobarbital or pentobarbital in similar past studies. It is therefore somewhat disappointing to have failed to show even a trend in favor of the 100-mg. doses over placebo, particularly in the light of the report from Salter, Lodge-Patch, and Hare[5]; but sampling problems, the different populations and methods employed, and the relative imprecision of studies of this type may explain the discrepancies between the English study and the present one. Our data would not justify their conclusions that thalidomide is three times as "potent" as secobarbital in terms of amount of drug required to produce a given effect. Our own guess would be that the two drugs are about equipotent. We do agree, however, with their observation that the drug is capable of producing hangover and other side effects, with an incidence in our experience roughly comparable to that seen with equal doses of secobarbital or pentobarbital. Only further comparative trials of thalidomide and standard drugs will define the appropriate niche of this new agent in the treatment of insomnia, but the data reported so far suggest that thalidomide is a drug worth trying in patients whose therapeutic needs cannot be met by older drugs. The drug has not as yet been reported to produce euphoria, and there is one report in which it is stated that a patient has taken 2.1 Gm. of drug without suffering severe consequences.[9] A British report[10] on the ability of thalidomide to inhibit uptake of radioactive iodine by the thyroid has been denied by another group of investigators.[11] The evidence available to date is therefore encouraging and arouses hope that thalidomide may represent a significant advance in hypnotic therapy, but wider experience is needed to define precisely the addiction liability and safety margin of the drug in man.

SUMMARY

Thalidomide has been evaluated in the treatment of insomnia in medical and surgical inpatients. The performance of 100-mg. doses was not significantly different from that of placebo. Doses of 200 mg., however, proved effective in inducing and maintaining sleep in the majority of patients and were significantly better in these regards than either placebo or 100-mg. doses. Administration of drug was associated with a higher incidence of side effects than was administration of placebo.

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A SIMPLE METHOD FOR DETERMINING STANDARD ERRORS OF SURVIVAL RATES, WITH TABLES

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PHYSICIANS have for a long time computed survival rates for chronic disease patients. Cancer, with its well-known 5-year survival rate, is perhaps the outstanding example, but survival has been measured in heart disease, tuberculosis, venereal disease, etc. Methods of survival analysis have also been applied to such diverse subjects as mice, vacuum tubes, tumblers, and milk bottles.

Two standard methods are available for computing survival rates: (1) the *direct* method and (2) the *life table*, or *actuarial*, method. Berkson and Gage[1,2] have given detailed directions for applying the direct method, as have Merrell and Shulman[3] and Cutler and Ederer[4] for the life table method. We will briefly describe the two methods. The purpose of this article is to make available a simple and rapid method, which requires no computing, only looking up values (standard errors) in a table, for evaluating the statistical reliability of survival rates computed by the direct method (Appendix A) and by maximum utilization of the life table method (Appendix B). The importance of evaluating statistical reliability along with survival rates will be explained.

Many articles on survival analysis appear in the medical literature each year. Few of these show standard errors or confidence intervals along with the survival rates. Many show the number of cases, which, when the direct method for computing survival rates has been used, enables the reader to compute the standard error from the formula $\sqrt{P_t\,(1 - P_t)/n}$ or otherwise evaluate the statistical reliability from tables.[5] When the life table method has been used, the number of cases alone, as Appendix B will show, does not enable the reader to evaluate the statistical reliability, because so much depends on the number of years over which the cases were entered into the study. Greenwood's formula, the commonly accepted method for calculating the standard error of the survival rate computed by the life table method,[2-4] is considerably more complex than $\sqrt{P_t\,(1 - P_t)/n}$

*End Results Evaluation Section.

TABLE I. SURVIVAL DATA FOR SINGLE YEAR COHORTS

YEARS AFTER ENTRY	ALIVE AT BEGINNING OF INTERVAL	DIED DURING INTERVAL	LOST TO FOLLOW-UP DURING INTERVAL	WITHDRAWN ALIVE DURING INTERVAL
x to x + 1	l_x	d_x	u_x	w_x
(1)	(2)	(3)	(4)	(5)
Patients entering in 1954 (1954 cohort)				
0–1	55	5	1	—
1–2	49	5	1	—
2–3	43	5	1	—
3–4	37	5	1	—
4–5	31	5	1	—
5–6	25	3	1	21
Patients entering in 1955 (1955 cohort)				
0–1	55	5	1	—
1–2	49	5	1	—
2–3	43	5	1	—
3–4	37	5	1	—
4–5	31	3	1	27
Patients entering in 1956 (1956 cohort)				
0–1	55	5	1	—
1–2	49	5	1	—
2–3	43	5	1	—
3–4	37	3	1	33
Patients entering in 1957 (1957 cohort)				
0–1	55	5	1	—
1–2	49	5	1	—
2–3	43	3	1	39
Patients entering in 1958 (1958 cohort)				
0–1	55	5	1	—
1–2	49	3	1	45
Patients entering in 1959 (1959 cohort)				
0–1	55	3	1	51

and requires the use of the detailed life table data which are not usually made available to the reader of articles on survival. Appendix B provides a source in which to look up immediately standard errors of 1-, 3-, and 5-year survival rates

TABLE II. COMPUTATION OF SURVIVAL RATES BY THE LIFE TABLE METHOD

YEARS AFTER DIAGNOSIS	ALIVE AT BEGINNING OF INTERVAL	DIED DURING INTERVAL	LOST TO FOLLOW-UP DURING INTERVAL	WITHDRAWN ALIVE DURING INTERVAL	EFFECTIVE NUMBER EXPOSED TO THE RISK OF DYING (COL. 2 − ½ COL. 4 − ½ COL. 5)	PROPORTION WHO DIED (COL. 3/COL. 6)	PROPORTION WHO SURVIVED (1 − COL. 7)	CUMULATIVE PROPORTION WHO SURVIVED FROM DIAGNOSIS THROUGH END OF INTERVAL ($p_1 \times p_2 \times \ldots \times p_x$)
x to x + 1	l_x	d_x	u_x	w_x	l'_x	q_x	p_x	P_x
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0–1	330	28	6	51	301.5	0.09	0.91	0.91
1–2	245	23	5	45	220.0	0.10	0.90	0.82
2–3	172	18	4	39	150.5	0.12	0.88	0.72
3–4	111	13	3	33	93.0	0.14	0.86	0.62
4–5	62	8	2	27	47.5	0.17	0.83	0.51
5–6	25	3	1	21				

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without knowledge of the detailed life table data. Tables in a previous article by the author[6] make it possible to calculate rapidly standard errors of 1-, 2-, 3-, . . . 10-year survival rates computed by the life table method.

THE DIRECT AND LIFE TABLE METHODS FOR COMPUTING SURVIVAL RATES

Consider a breast cancer series which began on Jan. 1, 1954. We measure survival on each patient from the date of diagnosis* and attempt to determine survival status once a year. Assume, for simplicity, that 55 patients entered the series during each calendar year and that, for each yearly cohort of 55 patients, 5 died and 1 was lost to follow-up during each year of follow-up, except that during the last year of follow-up (an incomplete year of follow-up for all cohorts), only 3 patients died. We tally all available information as of Dec. 31, 1959, and proceed to compute the 1-, 3-, and 5-year survival rates. Table I describes the follow-up history of the six yearly cohorts, 1954 to 1959. Note that the annual intervals shown in the first column are not calendar years. The intervals are measured from the date of diagnosis for each patient. The last column of the table shows the number of patients alive on the closing date of the study.

Using the direct method to compute the 1-year survival rate, we have to exclude the last cohort (1959), because it is necessary to limit the material to patients who have had the opportunity to survive for at least 1 year; the patients who entered in 1959 had been observed for less than 1 year on Dec. 31, 1959. We therefore add up the 1-year survival information of the 1954 to 1958 cohorts: 275 cases, 25 deaths, and 5 losses to follow-up. What do we do about the 5 cases lost to follow-up? No truly satisfactory method is available for handling these cases in the arithmetic; we do not know whether the survival experience of the lost cases is better than, worse than, or equal to the cases not lost. "The only correct method of handling persons lost to follow-up is not to have any."[7] Assuming the survival experience of the lost cases to be equal to that of the cases not lost, we exclude the lost cases from the calculation, and obtain $25/270 = 0.09$ as the proportion dying in 1 year and, therefore, $1.00 - 0.09 = 0.91$ (91 per cent) as the 1-year survival rate. To compute the 3-year survival rate by the direct method we have to exclude cases that were entered less than 3 years before the closing date and therefore limit the material to the 1954 to 1956 cohorts. Proceeding as before, we obtain $45/156 = 0.27$ as the proportion dying in 3 years and a 3-year survival rate of 0.73. Similarly, the 5-year survival rate is computed from the 1954 cohort as $1.00 - (25/50) = 0.50$. Note that a large proportion of the cases (nearly 10 per cent) was lost to follow-up and excluded from the calculation of the 5-year survival rate. If we assume that all the cases lost have a survival of 5 years, the survival rate is 0.54. If we assume that all the patients lost died within 5 years, the survival rate is only 0.45. The large disparity between these two extreme results emphasizes the importance of reducing the number of lost cases to a minimum.

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*Other starting dates are possible, e.g., date of admission or date of treatment.

The life table method permits us to use the available survival information on all the patients, even those who entered the series less than the required number of years before the closing date. We therefore sum the data on all six cohorts in Table I cell by cell and obtain the first five columns of Table II. Columns 6 through 9 of Table II show how the survival rates are computed. In column 6 we adjust the number of patients alive at the beginning of each annual interval for the number of patients lost and withdrawn alive during that interval. We assume those lost and withdrawn alive are exposed to the risk of dying, on the average, for one-half the interval and also that the survival experience of these patients subsequent to date of last contact is similar to that of those with complete follow-up information. Column 7 shows the proportion who died during each year of follow-up, and column 8, the proportion who survived. Column 9 cumulates the proportions who survived of column 8 and shows the proportion who survived from date of entry to the end of each of the 5 years of follow-up, i.e., the 1-, 2-, 3-, 4-, and 5-year survival rates. Thus, the fifth line of column 9 shows the 5-year survival rate (51 per cent), and we have obtained the 1-, 2-, 3-, and 4-year survival rates as by-products of calculating the 5-year rate.

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TABLE III

SURVIVAL RATE	DIRECT METHOD	LIFE TABLE METHOD
1-year	0.91	0.91
3-year	0.73	0.72
5-year	0.50	0.51

We note some difference in the results obtained by the two methods in Table III. This is explained in part by a difference in the basic data* and in part by a difference in assumption about the lost cases.† More important than the difference in computed values is that the rate computed by the life table method has smaller sampling variation, i.e., is statistically more reliable.[4]

SAMPLING VARIATION AND STATISTICAL RELIABILITY

Anyone who has made hemoglobin counts is familiar with *sampling variation*, or, as it is sometimes called, *chance variation* or *sampling error*. Successive hemoglobin determinations from a single blood sample can easily vary from, say, 13.9 to 14.3 Gm. per 100 ml. Admittedly, the hemoglobinometer is not the most precise measuring instrument. However, no measuring device is immune to

*The survival experience during the last year of follow-up, which was included in the life table calculations but excluded from the direct method calculations, is different from the survival experience for prior survival years.

†In applying the direct method we discarded the lost cases entirely. In applying the life table method we retained the lost cases until the date of last contact and then discarded them.

sampling variation. For example, 100 micrometer measurements on the thickness of the same steel strip made by the same experienced inspector varied between 0.0408 and 0.0420 inches.[8]

Consider another sampling experiment in which a "true" coin is repeatedly tossed into the air. On the average, we would expect 50 per cent "heads." Thus, if we made ten tosses, we would expect five heads. Yet, we would not think that a result of seven heads, i.e., 70 per cent, is very unusual. We would attribute the difference between the expected and the observed results to chance variation. If, however, we obtained 70 per cent heads in 10,000 tosses, we would suspect the trueness of the coin. The larger the number of observations, the smaller the probability of a given deviation from the expected proportion; or, to put it another way, as the sample size increases, sampling variation decreases and statistical reliability increases. This holds true for laboratory measurements, coin tossing, and also survival rates.

Let us consider one more example of sampling variation, this time using survival rates. We have obtained a 60 per cent 5-year survival rate in treating a long series of breast cancer patients. We have more recently applied a new treatment method to a series of 50 patients and obtain 70 per cent 5-year survival. Is this a truly superior result, or is this within range of sampling variation around 60 per cent? To answer this question, we have to understand some statistical theory, i.e., standard errors and confidence intervals.

The Standard Error and Confidence Intervals.—The standard error is a measure of sampling variation and, therefore, of statistical reliability. For example, the standard error of a survival rate of 70 per cent based on a sample of 100, computed by the direct method, is 4.5 per cent; based on a sample of 200, the standard error is 3.2 per cent; and based on a sample of 500, it is 2.0 per cent. The larger the sample, the smaller is the standard error, the greater is the reliability.

Universe values: To apply measures of sampling variation and statistical reliability to biologic problems, we postulate the existence of universe values, which are alternately referred to as "population values," "population parameters," or "parameters." Examples of universe values are: the 5-year survival rate for breast cancer in the United States, the blood count of a specific person on a given day, the probability of a head in tossing a coin, and the infant mortality rate in Japan in 1950. Universes can be either finite or infinite. The number of blood determinations one can make on a single sample of blood on a single day is finite, as is the number of breast cancer cases treated in a given hospital this year or the number of infants born in Japan in 1950. In biologic applications, however, we usually think of an *infinite* universe, e.g., all possible blood determinations that can be made on a single sample of blood in a day, all possible tosses of a coin, all possible breast cancer cases treated in a given hospital this year, or all possible infants born in Japan in 1950. We think of the infinite universe in biology rather than the finite universe, because our fundamental interest is not in, say, the specific blood count obtained in a single reading, but in the true blood count of the individual. Similarly, in evaluating a new breast cancer treatment, we want to

know how successful the treatment would be for all possible breast cancer patients and not what its result on a few individuals happened to be.

The infinite universe is, of course, a theoretic concept, and therefore we cannot determine the universe value precisely. In practice, we draw a sample consisting of a finite number of individuals, or observations, from the universe; from the sample, we estimate the universe value. Statistical methods permit us to draw, from the sample value, an inference regarding the range within which the universe value is likely to lie. This range is called a "confidence interval." The greater the number of observations, i.e., the larger the sample, the greater is the reliability of the estimate, therefore, the narrower is the confidence interval.

Confidence intervals: By adding and subtracting 1.96 times, or approximately *twice*, the standard error to and from a normally distributed* *sample* value, one obtains a 95 per cent confidence interval for the universe value. Using the previous example of a standard error of 4.5 per cent for a survival rate of 70 per cent (based on 100 patients and computed by the direct method), we obtain a 95 per cent confidence interval of $70 \pm 2 \times 4.5$, or 61 to 79 per cent. This means we are 95 per cent certain that the universe survival rate lies between 61 and 79. By adding and subtracting *once* the standard error, we obtain an approximate 68 per cent confidence interval, and by adding and subtracting 2.58 times the standard error, we obtain an approximate 99 per cent confidence interval. The tables of Appendices A and B give *twice* the standard error of the survival rate because the 95 per cent confidence interval is used more often than any of the others.

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*The word "normal" is used in the statistical sense. For an explanation of the normal distribution, sometimes called the "bell-shaped" distribution, see any standard statistical text. Many distributions encountered in natural and social science are approximately normal. Also, many sampling distributions, i.e., distributions of sampled values, are approximately normal. For instance, the proportion, or percentage of individuals having a given attribute (e.g., proportion or percentage surviving) is approximately normally distributed.

APPENDIX A

Direct Method

Table A applies to survival rates computed by the direct method. The values in this table do not depend on the time period for which the survival rate is computed; they apply equally to the 6-month survival rate and the 10-year rate. The values were computed from the formula for the standard error of a proportion, $\sqrt{P(1-P)/n}$, and give reasonably accurate confidence intervals for large values of n and values of P_t not near zero or 1.00. For low values of n and extreme values of P_t, the confidence intervals constructed from standard errors of P_t should not be taken literally but merely as guides to the reliability of the computed rate.

We will illustrate the use of Table A with the 3- and 5-year survival rates computed by the direct method earlier (from Table I).

1. The 3-year rate is 0.73, based on 156 cases. The rate nearest to 0.73 tabulated in table A is 0.70, and the number of cases nearest to 156 is 150. The value of twice the standard error corresponding to $P_t = 0.70$ and $n = 150$ is 0.07. Thus, the 95 per cent confidence interval is 0.73 ± 0.07, or 0.66 to 0.80. *It is not necessary to interpolate.* The tabled values will generally yield sufficient accuracy.

2. The 5-year rate is 0.50, based on 50 cases. $P_t = 0.50$ and $n = 50$ are both shown exactly in the stub and heading of the table. The value of twice the standard error is 0.14, yielding a 95 per cent confidence interval of 0.50 ± 0.14, or 0.36 to 0.64.

TABLE A. VALUES OF TWICE THE STANDARD ERROR FOR t-YEAR SURVIVAL RATES COMPUTED BY THE DIRECT METHOD*

NUMBER OF CASES (n)	t-YEAR SURVIVAL RATE (P_t)												
	.05	.10	.15	.20	.30	.40	.50	.60	.70	.80	.85	.90	.95
50	.06	.08	.10	.11	.13	.14	.14	.14	.13	.11	.10	.08	.06
60	.06	.08	.09	.10	.12	.13	.13	.13	.12	.10	.09	.08	.06
75	.05	.07	.08	.09	.11	.11	.12	.11	.11	.09	.08	.07	.05
100	.04	.06	.07	.08	.09	.10	.10	.10	.09	.08	.07	.06	.04
150	.04	.05	.06	.07	.07	.08	.08	.08	.07	.07	.06	.05	.04
200	.03	.04	.05	.06	.06	.07	.07	.07	.06	.06	.05	.04	.03
300	.03	.03	.04	.05	.05	.06	.06	.06	.05	.05	.04	.03	.03
400	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
500	.02	.03	.03	.04	.04	.04	.04	.04	.04	.04	.03	.03	.02
700	.02	.02	.03	.03	.03	.04	.04	.04	.03	.03	.03	.02	.02
1,000	.01	.02	.02	.03	.03	.03	.03	.03	.03	.03	.02	.02	.01
2,000	.01	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01

*Tabled values do not depend on the value of t.

APPENDIX B

Life Table Method

Tables B_1, B_2, and B_3 apply to rates computed by "maximum utilization" of the life table method, i.e., by the use of all information on survival available at the closing date of the study. Specifically, Table B_1 applies to the 1-year survival rate, Table B_2 to the 3-year rate, and Table B_3 to the 5-year rate. Any other time unit, such as day, week, or month, can be substituted for year provided the life table from which the survival rate was computed was organized in equal units of this size. The values in Tables B_1, B_2, and B_3 were computed from an approximation[6] to

Greenwood's formula.[9] The approximation assumes that the cases were entered into the study at a uniform rate and that the mortality rate is constant for each year of follow-up. However, the approximation has been shown to be acceptable even when the facts do not adhere closely to the assumptions, as, for examples, in cancer, where incidence is increasing for some sites and decreasing for others and where successive annual mortality rates decrease sharply.[6] Tables B_1, B_2, and B_3 may not be applicable when the incidence has changed radically during the study period, as for example when a hospital has added or lost sources of patients or when a central registry has markedly increased or decreased the number of reporting hospitals. Tables B_1, B_2, and B_3 do not apply when additional follow-up information has been included subsequent to the interval during which the last patient was entered into the study. When Tables B_1, B_2, and B_3 are not applicable, Greenwood's[3,4] formula may be used.

Each of the tables is subdivided into several sections according to Y, the number of years during which cases were entered into the study. For example, Table B_3 has six sections: $Y = 3$, 4, 5, 6, 9, and 15. The table shows that the section $Y = 6$ applies to $Y = 6$ or 7, that $Y = 9$ applies to $Y = 8$ through 11, and that $Y = 15$ applies to $Y = 12$ through 20. When Y exceeds 20, Table A may be used in place of Tables B_1, B_2, and B_3.

We will illustrate the use of Tables B_1, B_2, and B_3 by considering the 1-, 3-, and 5-year survival rates computed in Table II. All three rates are based on 330 cases ($n = 330$) entered over a 6-year period, 1954 to 1959 ($Y = 6$).

1. The 1-year survival rate is 0.91. We look in Table B_1 under the nearest tabled values of P_1, n, and Y, i.e., $P_1 = 0.90$, $n = 300$, and $Y = 4$ (3 through 20), and obtain the value 0.04 for twice the standard error of the survival rate. Again, as in Table A, it is not necessary to interpolate because the tabled values will usually give sufficient accuracy. Our 95 per cent confidence interval for the 1-year rate is 0.87 to 0.95.

2. The 3-year survival rate is 0.72. We look in Table B_2 under $P_3 = 0.70$, $n = 300$, and $Y = 6$ and obtain the value 0.06 for twice the standard error; this yields the confidence interval 0.66 to 0.78.

3. The 5-year survival rate is 0.51. We look in Table B_3 under $P_5 = 0.50$, $n = 300$, and $Y = 6$ and obtain the value 0.09, which yields the confidence interval 0.42 to 0.60.

Note here that the 3-year survival rate computed by the life table method, as indicated by twice the standard error, is somewhat more reliable than that computed by the direct method (0.06 versus 0.07). For the 5-year rate, the gain in using the life table method is more substantial (0.09 versus 0.14). The 3- and 5-year rates computed by the life table method are each based on patients diagnosed over a 6-year period (1954 to 1959). The 3-year rate computed by the direct method is based on patients diagnosed over a 3-year period (1954 to 1956), and the 5-year rate computed by the direct method is based on patients diagnosed during 1 year only (1954).

For reasons similar to those given for Table A, confidence limits obtained from Tables B_1, B_2, and B_3 are not exact, especially those for low values of n and extreme values of P_t. Whereas exact confidence intervals for rates computed by the direct method are available, no exact standard errors or confidence intervals are available for rates computed by "maximum utilization" of the life table method. The values in the following tables, although not exact, will serve well as an index to the statistical reliability of survival rates computed by the life table method.

An inspection of Tables A, B_1, B_2, and B_3 will show that survival rates based on as few as 50 or 100 cases are not very reliable. Thus, the value of twice the standard error for a rate of 0.40 computed by the direct method based on 50 cases is 0.14; based on 100 cases, 0.10. This means that in the former case the true survival rate could easily be between 0.26 and 0.54 and in the latter case between 0.30 and 0.50. Rates for corresponding values of n and P_t computed by the life table method are even less reliable, because some of the patients included in the computation were not exposed to the risk of dying for the full period.* Standard error values based on less than 50 cases are not shown, because rates based on less than 50 cases are too unreliable to be of great value.

*This should not be interpreted as a contradiction of our previous observation that the life table method will tend to produce more reliable survival rates.

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TABLE B_1. APPROXIMATE VALUES OF TWICE THE STANDARD ERROR FOR 1-YEAR SURVIVAL RATES COMPUTED BY THE LIFE TABLE METHOD

NUMBER OF CASES (n)	1-YEAR SURVIVAL RATE (P_1)												
	.05	.10	.15	.20	.30	.40	.50	.60	.70	.80	.85	.90	.95
Y = 1 (1 year in which cases were entered into the study)													
50	.06	.09	.11	.12	.15	.16	.17	.17	.17	.15	.14	.12	.08
60	.06	.08	.10	.11	.13	.15	.16	.16	.15	.14	.13	.11	.08
75	.05	.07	.09	.10	.12	.13	.14	.14	.14	.12	.11	.10	.07
100	.04	.06	.08	.09	.10	.12	.12	.12	.12	.11	.10	.08	.06
150	.04	.05	.06	.07	.08	.10	.10	.10	.10	.09	.08	.07	.05
200	.03	.04	.05	.06	.07	.08	.09	.09	.08	.08	.07	.06	.04
300	.03	.04	.04	.05	.06	.07	.07	.07	.07	.06	.06	.05	.03
400	.02	.03	.04	.04	.05	.06	.06	.06	.06	.05	.05	.04	.03
500	.02	.03	.03	.04	.05	.05	.06	.06	.05	.05	.04	.04	.03
700	.02	.02	.03	.03	.04	.04	.05	.05	.05	.04	.04	.03	.02
1,000	.01	.02	.02	.03	.03	.04	.04	.04	.04	.03	.03	.03	.02
2,000	.01	.01	.02	.02	.02	.03	.03	.03	.03	.02	.02	.02	.01
Y = 2 (2 years in which cases were entered into the study)													
50	.06	.08	.11	.12	.14	.15	.15	.15	.14	.13	.12	.10	.07
60	.06	.08	.10	.11	.13	.14	.14	.14	.13	.12	.11	.09	.06
75	.05	.07	.09	.10	.11	.12	.13	.13	.12	.11	.10	.08	.06
100	.04	.06	.07	.08	.10	.11	.11	.11	.10	.09	.08	.07	.05
150	.04	.05	.06	.07	.08	.09	.09	.09	.08	.07	.07	.06	.04
200	.03	.04	.05	.06	.07	.07	.08	.08	.07	.06	.06	.05	.03
300	.03	.03	.04	.05	.06	.06	.06	.06	.06	.05	.05	.04	.03
400	.02	.03	.04	.04	.05	.05	.05	.05	.05	.05	.04	.03	.02
500	.02	.03	.03	.04	.04	.05	.05	.05	.05	.04	.04	.03	.02
700	.02	.02	.03	.03	.04	.04	.04	.04	.04	.03	.03	.03	.02
1,000	.01	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03	.02	.02
2,000	.01	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
Y = 4 (3 through 20 years in which cases cases were entered into the study)*													
50	.06	.08	.10	.12	.13	.14	.15	.14	.14	.12	.11	.09	.06
60	.06	.08	.09	.11	.12	.13	.13	.13	.12	.11	.10	.08	.06
75	.05	.07	.08	.10	.11	.12	.12	.12	.11	.10	.09	.07	.05
100	.04	.06	.07	.08	.09	.10	.10	.10	.10	.08	.07	.06	.04
150	.04	.05	.06	.07	.08	.08	.08	.08	.08	.07	.06	.05	.04
200	.03	.04	.05	.06	.07	.07	.07	.07	.07	.06	.05	.04	.03
300	.03	.03	.04	.05	.05	.06	.06	.06	.06	.05	.04	.04	.03
400	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.03	.03	.02
500	.02	.03	.03	.04	.04	.05	.05	.05	.04	.04	.03	.03	.02
700	.02	.02	.03	.03	.04	.04	.04	.04	.04	.03	.03	.02	.02
1,000	.01	.02	.02	.03	.03	.03	.03	.03	.03	.03	.02	.02	.01
2,000	.01	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01

*When Y exceeds 20, use Table A.

TABLE B_2. APPROXIMATE VALUES OF TWICE THE STANDARD ERROR FOR 3-YEAR SURVIVAL RATES COMPUTED BY THE LIFE TABLE METHOD

NUMBER OF CASES (n)	3-YEAR SURVIVAL RATE (P_3)												
	.05	.10	.15	.20	.30	.40	.50	.60	.70	.80	.85	.90	.95
Y = 3 (3 years in which cases were entered into the study)													
50	.11	.15	.18	.20	.23	.25	.25	.24	.23	.20	.18	.15	.11
60	.10	.14	.17	.19	.21	.22	.23	.22	.21	.18	.16	.14	.10
75	.09	.12	.15	.17	.19	.20	.21	.20	.19	.16	.14	.12	.09
100	.08	.11	.13	.14	.16	.17	.18	.17	.16	.14	.12	.11	.08
150	.07	.09	.10	.12	.13	.14	.15	.14	.13	.12	.10	.09	.06
200	.06	.08	.09	.10	.12	.12	.13	.12	.11	.10	.09	.07	.05
300	.05	.06	.07	.08	.09	.10	.10	.10	.09	.08	.07	.06	.04
400	.04	.05	.06	.07	.08	.09	.09	.09	.08	.07	.06	.05	.04
500	.04	.05	.06	.06	.07	.08	.08	.08	.07	.06	.06	.05	.03
700	.03	.04	.05	.05	.06	.07	.07	.07	.06	.05	.05	.04	.03
1,000	.03	.03	.04	.05	.05	.05	.06	.05	.05	.04	.04	.03	.02
2,000	.02	.02	.03	.03	.04	.04	.04	.04	.04	.03	.03	.02	.02
Y = 4 (4 years in which cases were entered into the study)													
50	.09	.12	.14	.16	.18	.19	.19	.19	.17	.15	.14	.11	.08
60	.08	.11	.13	.14	.16	.17	.18	.17	.16	.14	.12	.10	.08
75	.07	.10	.12	.13	.15	.15	.16	.15	.14	.12	.11	.09	.07
100	.06	.08	.10	.11	.13	.13	.14	.13	.12	.11	.10	.08	.06
150	.05	.07	.08	.09	.10	.11	.11	.11	.10	.09	.08	.07	.05
200	.04	.06	.07	.08	.09	.09	.10	.09	.09	.08	.07	.06	.04
300	.04	.05	.06	.06	.07	.08	.08	.08	.07	.06	.06	.05	.03
400	.03	.04	.05	.06	.06	.07	.07	.07	.06	.05	.05	.04	.03
500	.03	.04	.04	.05	.06	.06	.06	.06	.06	.05	.04	.04	.03
700	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
1,000	.02	.03	.03	.04	.04	.04	.04	.04	.04	.03	.03	.03	.02
2,000	.01	.02	.02	.02	.03	.03	.03	.03	.03	.02	.02	.02	.01
Y = 5 (5 years in which cases were entered into the study)													
50	.08	.11	.13	.14	.16	.17	.18	.17	.16	.14	.12	.11	.07
60	.07	.10	.12	.13	.15	.16	.16	.16	.15	.13	.11	.10	.07
75	.07	.09	.10	.12	.13	.14	.14	.14	.13	.11	.10	.09	.06
100	.06	.08	.09	.10	.11	.12	.12	.12	.11	.10	.09	.07	.05
150	.05	.06	.07	.08	.09	.10	.10	.10	.09	.08	.07	.06	.04
200	.04	.05	.06	.07	.08	.09	.09	.09	.08	.07	.06	.05	.04
300	.03	.04	.05	.06	.07	.07	.07	.07	.07	.06	.05	.04	.03
400	.03	.04	.04	.05	.06	.06	.06	.06	.06	.05	.04	.04	.03
500	.03	.03	.04	.05	.05	.06	.06	.05	.05	.04	.04	.03	.02
700	.02	.03	.03	.04	.04	.05	.05	.05	.04	.04	.03	.03	.02
1,000	.02	.02	.03	.03	.04	.04	.04	.04	.04	.03	.03	.02	.02
2,000	.01	.02	.02	.02	.03	.03	.03	.03	.03	.02	.02	.02	.01

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TABLE B_2. APPROXIMATE VALUES OF TWICE THE STANDARD ERROR FOR 3-YEAR SURVIVAL RATES COMPUTED BY THE LIFE TABLE METHOD—(CONT'D)

NUMBER OF CASES (n)	3-YEAR SURVIVAL RATE (P_3)												
	.05	.10	.15	.20	.30	.40	.50	.60	.70	.80	.85	.90	.95
Y = 6 (6 or 7 years in which cases were entered into the study)													
50	.07	.10	.12	.14	.15	.16	.17	.16	.15	.13	.12	.10	.07
60	.07	.09	.11	.12	.14	.15	.15	.15	.14	.12	.11	.09	.07
75	.06	.08	.10	.11	.13	.13	.14	.13	.12	.11	.10	.08	.06
100	.05	.07	.08	.10	.11	.12	.12	.12	.11	.09	.08	.07	.05
150	.04	.06	.07	.08	.09	.10	.10	.10	.09	.08	.07	.06	.04
200	.04	.05	.06	.07	.08	.08	.08	.08	.08	.07	.06	.05	.04
300	.03	.04	.05	.06	.06	.07	.07	.07	.06	.05	.05	.04	.03
400	.03	.04	.04	.05	.05	.06	.06	.06	.05	.05	.04	.03	.03
500	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
700	.02	.03	.03	.04	.04	.04	.04	.04	.04	.04	.03	.03	.02
1,000	.02	.02	.03	.03	.03	.04	.04	.04	.03	.03	.03	.02	.02
2,000	.01	.02	.02	.02	.02	.03	.03	.03	.02	.02	.02	.02	.01
Y = 9 (8 through 11 years in which cases were entered into the study)													
50	.07	.09	.11	.13	.14	.15	.16	.15	.14	.13	.11	.09	.07
60	.06	.09	.10	.12	.13	.14	.14	.14	.13	.12	.10	.09	.06
75	.06	.08	.09	.10	.12	.13	.13	.12	.12	.10	.09	.08	.06
100	.05	.07	.08	.09	.10	.11	.11	.11	.10	.09	.08	.07	.05
150	.04	.05	.07	.07	.08	.09	.09	.09	.08	.07	.07	.05	.04
200	.03	.05	.06	.06	.07	.08	.08	.08	.07	.06	.06	.05	.03
300	.03	.04	.05	.05	.06	.06	.06	.06	.06	.05	.05	.04	.03
400	.02	.03	.04	.04	.05	.05	.06	.05	.05	.04	.04	.03	.02
500	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
700	.02	.02	.03	.03	.04	.04	.04	.04	.04	.03	.03	.02	.02
1,000	.02	.02	.03	.03	.03	.03	.04	.03	.03	.03	.03	.02	.02
2,000	.01	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01
Y = 15 (12 through 20 years in which cases were entered into the study)*													
50	.06	.09	.11	.12	.14	.15	.15	.15	.14	.12	.11	.09	.06
60	.06	.08	.10	.11	.13	.13	.14	.13	.13	.11	.10	.08	.06
75	.05	.07	.09	.10	.11	.12	.12	.12	.11	.10	.09	.07	.05
100	.04	.06	.07	.08	.10	.10	.11	.10	.10	.08	.07	.06	.04
150	.04	.05	.06	.07	.08	.08	.09	.08	.08	.07	.06	.05	.04
200	.03	.04	.05	.06	.07	.07	.07	.07	.07	.06	.05	.04	.03
300	.03	.04	.04	.05	.06	.06	.06	.06	.06	.05	.04	.04	.03
400	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
500	.02	.03	.03	.04	.04	.05	.05	.05	.04	.04	.03	.03	.02
700	.02	.02	.03	.03	.04	.04	.04	.04	.04	.03	.03	.02	.02
1,000	.01	.02	.02	.03	.03	.03	.03	.03	.03	.03	.02	.02	.01
2,000	.01	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01

*When Y exceeds 20, use Table A.

TABLE B_5. APPROXIMATE VALUES OF TWICE THE STANDARD ERROR FOR 5-YEAR SURVIVAL RATES COMPUTED BY THE LIFE TABLE METHOD

NUMBER OF CASES (n)	5-YEAR SURVIVAL RATE (P_5)												
	.05	.10	.15	.20	.30	.40	.50	.60	.70	.80	.85	.90	.95
Y = 5 (5 years in which cases were entered into the study)													
50	.14	.18	.22	.24	.27	.28	.28	.27	.25	.22	.19	.16	.12
60	.12	.17	.20	.22	.24	.26	.26	.25	.23	.20	.18	.15	.11
75	.11	.15	.18	.19	.22	.23	.23	.22	.21	.18	.16	.13	.10
100	.10	.13	.15	.17	.19	.20	.20	.19	.18	.15	.14	.11	.08
150	.08	.11	.12	.14	.15	.16	.16	.16	.15	.13	.11	.09	.07
200	.07	.09	.11	.12	.13	.14	.14	.14	.13	.11	.10	.08	.06
300	.06	.07	.09	.10	.11	.11	.11	.11	.10	.09	.08	.07	.05
400	.05	.06	.08	.08	.09	.10	.10	.10	.09	.08	.07	.06	.04
500	.04	.06	.07	.07	.08	.09	.09	.09	.08	.07	.06	.05	.04
700	.04	.05	.06	.06	.07	.07	.08	.07	.07	.06	.05	.04	.03
1,000	.03	.04	.05	.05	.06	.06	.06	.06	.06	.05	.04	.04	.03
2,000	.02	.03	.03	.04	.04	.04	.04	.04	.04	.03	.03	.03	.02
Y = 6 (6 years in which cases were entered into the study)													
50	.10	.14	.16	.18	.20	.21	.21	.21	.19	.16	.15	.12	.09
60	.09	.12	.15	.16	.18	.19	.19	.19	.18	.15	.13	.11	.08
75	.08	.11	.13	.14	.16	.17	.17	.17	.16	.13	.12	.10	.07
100	.07	.10	.11	.12	.14	.15	.15	.15	.14	.12	.10	.09	.06
150	.06	.08	.09	.10	.12	.12	.12	.12	.11	.10	.08	.07	.05
200	.05	.07	.08	.09	.10	.11	.11	.10	.10	.08	.07	.06	.04
300	.04	.06	.07	.07	.08	.09	.09	.08	.08	.07	.06	.05	.04
400	.04	.05	.06	.06	.07	.07	.08	.07	.07	.06	.05	.04	.03
500	.03	.04	.05	.06	.06	.07	.07	.06	.06	.05	.05	.04	.03
700	.03	.04	.04	.05	.05	.06	.06	.05	.05	.04	.04	.03	.02
1,000	.02	.03	.04	.04	.04	.05	.05	.05	.04	.04	.03	.03	.02
2,000	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03	.02	.02	.01
Y = 7 (7 years in which cases were entered into the study)													
50	.09	.12	.14	.16	.18	.19	.19	.19	.17	.15	.13	.11	.08
60	.08	.11	.13	.14	.16	.17	.18	.17	.16	.14	.12	.10	.07
75	.07	.10	.12	.13	.15	.15	.16	.15	.14	.12	.11	.09	.07
100	.06	.08	.10	.11	.13	.13	.14	.13	.12	.11	.09	.08	.06
150	.05	.07	.08	.09	.10	.11	.11	.11	.10	.09	.08	.07	.05
200	.04	.06	.07	.08	.09	.09	.10	.09	.09	.07	.07	.06	.04
300	.04	.05	.06	.06	.07	.08	.08	.08	.07	.06	.05	.05	.03
400	.03	.04	.05	.06	.06	.07	.07	.07	.06	.05	.05	.04	.03
500	.03	.04	.05	.05	.06	.06	.06	.06	.06	.05	.04	.04	.03
700	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
1,000	.02	.03	.03	.04	.04	.04	.04	.04	.04	.03	.03	.03	.02
2,000	.01	.02	.02	.02	.03	.03	.03	.03	.03	.02	.02	.02	.01

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TABLE B_3. APPROXIMATE VALUES OF TWICE THE STANDARD ERROR FOR 5-YEAR SURVIVAL RATES COMPUTED BY THE LIFE TABLE METHOD—(CONT'D)

NUMBER OF CASES (n)	5-YEAR SURVIVAL RATE (P_5)												
	.05	.10	.15	.20	.30	.40	.50	.60	.70	.80	.85	.90	.95
Y = 8 (8 years in which cases were entered into the study)													
50	.08	.11	.13	.15	.17	.18	.18	.18	.16	.14	.13	.11	.07
60	.08	.10	.12	.14	.15	.16	.17	.16	.15	.13	.12	.10	.07
75	.07	.09	.11	.12	.14	.15	.15	.14	.13	.12	.10	.09	.06
100	.06	.08	.09	.11	.12	.13	.13	.12	.12	.10	.09	.07	.05
150	.05	.07	.08	.09	.10	.10	.10	.10	.10	.08	.07	.06	.04
200	.04	.06	.07	.07	.08	.09	.09	.09	.08	.07	.06	.05	.04
300	.03	.05	.05	.06	.07	.07	.07	.07	.07	.06	.05	.04	.03
400	.03	.04	.05	.05	.06	.06	.06	.06	.06	.05	.04	.04	.03
500	.03	.04	.04	.05	.05	.06	.06	.06	.05	.04	.04	.03	.02
700	.02	.03	.04	.04	.04	.05	.05	.05	.04	.04	.03	.03	.02
1,000	.02	.03	.03	.03	.04	.04	.04	.04	.04	.03	.03	.02	.02
2,000	.01	.02	.02	.02	.03	.03	.03	.03	.03	.02	.02	.02	.01
Y = 10 (9 through 12 years in which cases were entered into the study)													
50	.07	.11	.12	.14	.16	.17	.17	.16	.15	.13	.12	.10	.07
60	.07	.10	.11	.13	.14	.15	.15	.15	.14	.12	.11	.09	.07
75	.06	.09	.10	.11	.13	.14	.14	.13	.13	.11	.10	.08	.06
100	.05	.07	.09	.10	.11	.12	.12	.12	.11	.09	.08	.07	.05
150	.04	.06	.07	.08	.09	.10	.10	.10	.09	.08	.07	.06	.04
200	.04	.05	.06	.07	.08	.08	.08	.08	.08	.07	.06	.05	.04
300	.03	.04	.05	.06	.06	.07	.07	.07	.06	.05	.05	.04	.03
400	.03	.04	.04	.05	.06	.06	.06	.06	.05	.05	.04	.03	.03
500	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
700	.02	.03	.03	.04	.04	.04	.05	.04	.04	.04	.03	.03	.02
1,000	.02	.02	.03	.03	.04	.04	.04	.04	.03	.03	.03	.02	.02
2,000	.01	.02	.02	.02	.02	.03	.03	.03	.02	.02	.02	.02	.01
Y = 15 (13 through 20 years in which cases were entered into the study)*													
50	.07	.10	.11	.13	.14	.15	.16	.15	.14	.13	.11	.09	.07
60	.06	.09	.10	.12	.13	.14	.14	.14	.13	.12	.10	.09	.06
75	.06	.08	.09	.10	.12	.13	.13	.13	.12	.10	.09	.08	.06
100	.05	.07	.08	.09	.10	.11	.11	.11	.10	.09	.08	.07	.05
150	.04	.06	.07	.07	.08	.09	.09	.09	.08	.07	.07	.05	.04
200	.03	.05	.06	.06	.07	.08	.08	.08	.07	.06	.06	.05	.03
300	.03	.04	.05	.05	.06	.06	.06	.06	.06	.05	.05	.04	.03
400	.02	.03	.04	.04	.05	.05	.06	.05	.05	.04	.04	.03	.02
500	.02	.03	.04	.04	.05	.05	.05	.05	.05	.04	.04	.03	.02
700	.02	.03	.03	.03	.04	.04	.04	.04	.04	.03	.03	.02	.02
1,000	.02	.02	.03	.03	.03	.03	.04	.03	.03	.03	.03	.02	.02
2,000	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01

*When Y exceeds 20, use Table A.

Announcements

THE 6TH INTERNATIONAL CONGRESS OF INTERNAL MEDICINE will be held Aug. 24 to 27, 1960 in Basle, Switzerland. The Congress has been organized by the International Society of Internal Medicine, Sir Russell Brain, F.A.C.P. Hon., London, President. The officers of the Congress are: Prof. A. Gigon, Basle, President; Prof. H. Ludwig, Basle, Secretary.

Panels on interstitial nephritis, nephrosis, diuretics, diagnostic value of enzymes, therapeutic indications for enzymes, serology in rheumatic diseases, and instruction in internal medicine will be held.

Seventy leading internists from all over the world will take part in the main scientific program by reading papers or joining in panel discussions.

The official languages will be German, French, and English. There will be simultaneous translation of the principal lectures.

Programs and registration forms for the Congress may be obtained from the Secretary, 6th International Congress of Internal Medicine, Steinentorstrasse 13, Basle 10, Switzerland.

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The International Association of Gerontology has selected San Francisco as the site for its FIFTH INTERNATIONAL CONGRESS OF GERONTOLOGY. The dates will be Aug. 7 to 12, 1960. On the basis of the interest already shown in the Congress, it is expected that between 1,500 and 2,000 persons, from every continent, will participate.

The program of the Congress will be planned in four sections: The Biological Sciences; Clinical Medicine; Psychology and the Social Sciences; and Social Welfare. Each section will hold six scientific sessions for the presentation of papers. These four scientific sessions will meet simultaneously. Each section's program committee will be responsible for planning a general symposium to be attended by all Congress participants. In addition, there will be two plenary sessions and at least one open, public meeting. In order to allow the widest possible latitude for the scientific papers, no over-all Congress theme was chosen. English will be the official language.

It is highly desirable that as many as possible register for the Congress well in advance of the opening date. The registration fee will be $25.00 for all who register before May 31, 1960; thereafter, the registration fee will be $30.00. Those desiring to register in advance should so inform the President of the Congress. They will be sent the necessary forms.

There will be ample space immediately adjacent to the meeting rooms for exhibits. All inquiries relative to commercial or scientific exhibits should be addressed to Dr. Leo Gitman, Chairman, Committee on Exhibits, Brooklyn Home for the Aged, Howard and Dumont Aves., Brooklyn 12, N. Y.

All general inquiries should be directed to Louis Kuplan, President, Fifth International Congress of Gerontology, P. O. Box 2103, Sacramento 10, Calif.

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